Clinical Policy: Obinutuzumab (Gazyva)
Reference Number: CP.PHAR.305
Effective Date: 02.01.17
Last Review Date: 11.19
Line of Business: Medicaid, HIM-Medical Benefit

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Obinutuzumab (Gazyva®) is a CD20-directed cytolytic antibody.

FDA Approved Indication(s)
Gazyva is indicated:

- In combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL)
- 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
- 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

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Gazyva is medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (must meet all):
      1. Diagnosis of CLL or small lymphocytic lymphoma (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: 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;
         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 MALT lymphoma;
      2) Nongastric MALT lymphoma;
ii. Histologic transformation of 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 Gazyva 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: 6 months

C. Other diagnoses/indications
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid and HIM-Medical Benefit.

II. Continued Therapy

A. All Indications in Section I (must meet all):
1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Gazyva for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. 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: 12 months

B. Other diagnoses/indications (must meet 1 or 2):
   1. Currently receiving medication via Centene benefit and documentation supports
      positive response to therapy.
      Approval duration: Duration of request or 6 months (whichever is less); or
   2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT
      specifically listed under section III (Diagnoses/Indications for which coverage is
      NOT authorized): CP.PMN.53 for Medicaid and HIM-Medical Benefit.

III. Diagnoses/Indications for which coverage is NOT authorized:
   A. Non-FDA approved indications, which are not addressed in this policy, unless there is
      sufficient documentation of efficacy and safety according to the off label use policies –
      CP.PMN.53 for Medicaid and HIM-Medical Benefit or evidence of coverage documents.

IV. Appendices/General Information
   Appendix A: Abbreviation/Acronym Key
   CLL: chronic lymphocytic leukemia          NCCN: National Comprehensive Cancer
   FDA: Food and Drug Administration          Network
   FL: follicular lymphoma                  NHL: non-Hodgkin lymphoma
   MALT: mucosa-associated lymphoid tissue  SLL: small lymphocytic lymphoma

   Appendix B: Therapeutic Alternatives
   This table provides a listing of preferred alternative therapy recommended in the approval
   criteria. The drugs listed here may not be a formulary agent for all relevant lines of business
   and may require prior authorization.

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

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

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

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL/SLL</td>
<td>100 mg IV on day 1, 900 mg IV on day 2 of cycle 1, then 1,000 mg IV on days 8 and 15 of cycle 1; begin the next cycle of therapy on day 29. For cycles 2 to 6, give obinutuzumab 1,000 mg IV on day 1 repeated every 28 days. Administer obinutuzumab in combination with chlorambucil (0.5 mg/kg orally on day 1 and 15) in cycles 1 to 6.</td>
<td>See regimen</td>
</tr>
<tr>
<td>FL</td>
<td>1,000 mg IV on day 1, 8 and 15 of Cycle 1, 1,000 mg on day 1 of Cycles 2-6 or Cycles 2-8, and then 1,000 mg every 2 months for up to 2 years. For patients with relapsed or refractory FL, administer Gazyva in combination with bendamustine in six 28-day cycles. Patients who achieve stable disease, complete response, or partial response to the initial 6 cycles should continue on Gazyva 1,000 mg as monotherapy for up to two years. For patients with previously untreated FL, administer Gazyva with one of the following chemotherapy regimens: • Six 28-day cycles in combination with bendamustine • Six 21-day cycles in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), followed by 2 additional 21-day cycles of Gazyva alone • Eight 21-day cycles in combination with CVP (cyclophosphamide, vincristine, prednisone) Patients with previously untreated FL who achieve a complete response or partial response to the initial 6 or 8 cycles should continue on Gazyva 1,000 mg as monotherapy for up to two years.</td>
<td>See regimen</td>
</tr>
</tbody>
</table>

VI. Product Availability
- Single-dose vial: 1,000 mg/40 mL (25 mg/mL)
VII. References

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

<table>
<thead>
<tr>
<th>HCPSC Codes</th>
<th>Description</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
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<tbody>
<tr>
<td>J9301</td>
<td>Injection, obinutuzumab, 10 mg</td>
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Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Policy split from CP.PHAR.182 Excellus Oncology.</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
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<tbody>
<tr>
<td>Age and dosing added</td>
<td>01.01.17</td>
<td>02.17</td>
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<tr>
<td>Safety information removed.</td>
<td>09.05.17</td>
<td>11.17</td>
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<tr>
<td>NCCN recommended uses added separately.</td>
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<tr>
<td>HCPCS code updated</td>
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<tr>
<td>4Q 2018 annual review: HIM-Medical Benefit added; summarized NCCN and FDA-approved uses for improved clarity; added specialist involvement in care; separated FL and off-label MZL into individual criteria sets; removed primary cutaneous B-cell lymphomas as a covered off-label indication (not listed in the NCCN compendium for Gazyva); updated continued therapy section to include language for continuity of care; references reviewed and updated.</td>
<td>07.16.18</td>
<td>11.18</td>
</tr>
<tr>
<td>4Q 2019 annual review: NCCN recommended uses added for B-cell lymphomas; FDA/NCCN dosing limitation added, references reviewed and updated.</td>
<td>08.27.19</td>
<td>11.19</td>
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</tbody>
</table>

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical
policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.