OVERVIEW
Bendamustine is an alkylating agent containing a bifunctional mechlorethamine derivative and a purine-like ring.1-3 Mechlorethamine and its derivatives develop electrophilic alkyl groups which covalently bond to electron-rich nucleophilic moieties, leading to interstrand crosslinking of DNA. The crosslinkage can lead to cell death by several different mechanisms, however, the exact mechanism of action of bendamustine is unknown.

Bendamustine is indicated for the treatment of patients with chronic lymphocytic leukemia.1-3 Efficacy compared to first-line agents other than chlorambucil has not been established.

Bendamustine is indicated for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within 6 months of treatment with rituximab or a rituximab containing regimen.1-3

GUIDELINES
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (v. 5.2019 – May 23, 2019) recommend bendamustine, in combination with rituximab (e.g., Rituxan, Truxima), Gazyva® (obinutuzumab injection for intravenous [IV] use), or Arzerra® (ofatumumab injection for IV use), for patients ≥ 65 years of age without del(17p)/TP53 mutation, or younger patients with or without significant comorbidities.4,5 Bendamustine in combination with rituximab is recommended for the treatment of relapsed or refractory disease without del(17p)/TP53 mutation in patients < 65 years of age without significant comorbidities.

B-Cell Lymphomas
The NCCN B-Cell Lymphomas Clinical Practice Guidelines (v. 4.2019 – June 18, 2019) recommend bendamustine for the treatment of a variety B-cell lymphomas, including follicular lymphoma (grade 1 – 2), gastric MALT lymphoma, nongastric MALT lymphoma, nodal marginal zone lymphoma, splenic marginal zone lymphoma, histologic transformation of marginal zone lymphoma to diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, DLBCL, high-grade B-cell lymphoma, acquired immunodeficiency syndrome (AIDS)-related B-cell lymphoma, and post-transplant lymphoproliferative disorders.3,5 Bendamustine is recommended as monotherapy, or in combination with rituximab, or Gazyva depending on the lymphoma type and previous treatment history.

Hodgkin Lymphoma
The NCCN Hodgkin Lymphoma Clinical Practice Guidelines (v. 1.2019 – April 9, 2019) recommends bendamustine for the treatment of recurrent or refractory classic Hodgkin Lymphoma.4,6 In patients ≥ 18 years of age, bendamustine in combination with gemcitabine and vinorelbine, or in combination with Adcetris® (brentuximab injection for IV use) is recommended for second-line or subsequent therapy (if not previously used), or as a single agent for subsequent therapy. In patients > 60 years of age, bendamustine is recommended as a single agent for palliative therapy of relapsed or refractory disease.
Multiple Myeloma
Bendamustine is recommended in the NCCN Multiple Myeloma Clinical Practice Guidelines (v. 3.2019 – June 19, 2019) as a treatment option for relapsed or progressive multiple myeloma. Bendamustine is recommended as a single agent, or in combination with dexamethasone and Revlimid® (lenalidomide capsules) or with dexamethasone and Velcade® (bortezomib injection for IV and subcutaneous use).4,12

Primary Cutaneous Lymphomas
The NCCN Primary Cutaneous Lymphomas Clinical Practice Guidelines (v. 2.2019 – December 17, 2018) recommend bendamustine for the systemic treatment of mycosis fungoides/Sezary syndrome with or without skin-directed or radiation therapy, and as a single agent for the treatment of relapsed/refractory primary cutaneous CD30+ T-cell lymphoproliferative disorders.4,27

T-Cell Lymphomas
The NCCN T-Cell Lymphomas Clinical Practice Guidelines (v. 2.2019 – December 17, 2018) recommend bendamustine as a single agent for the treatment of relapsed or refractory peripheral T-cell lymphomas, adult T-cell leukemia/lymphoma, and refractory hepatosplenic gamma-delta T-cell lymphoma after two primary treatment regimens.4,20

Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma
Bendamustine is recommended in the NCCN Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines (v. 2.2019 – September 14, 2018) as a single agent or in combination with rituximab (e.g., Rituxan, Truxima) for primary treatment, for the treatment of previously treated disease that did not respond, or for progressive or relapsed disease.4,22

POLICY STATEMENT
Prior authorization is recommended for medical benefit coverage of bendamustine. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with bendamustine as well as the monitoring required for adverse events and long-term efficacy, approval requires bendamustine to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of bendamustine is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Approve for 6 months if bendamustine is prescribed by or in consultation with an oncologist.

Dosing. Approve the following dosing:
A) Each individual dose must not exceed 100 mg/m² given by intravenous infusion; AND
B) The patient receives a maximum of two doses per 28-day cycle.1,3
Note: Dose modifications of bendamustine are recommended for the management of neutropenia, thrombocytopenia, and other non-hematological toxicity. This may include reducing the dose, withholding the drug until the toxicity is resolved, or discontinuing the drug all together. See the prescribing information for more detail.

2. **B-Cell Non-Hodgkin Lymphoma.** Approve for 6 months if bendamustine is prescribed by or in consultation with an oncologist.

**Dosing.** Approve the following dosing:
A) Each individual dose must not exceed 120 mg/m² given by intravenous infusion; AND
B) The patient receives a maximum of two doses per 21-day cycle.

Note: Dose modifications of bendamustine are recommended for the management of neutropenia, thrombocytopenia, and other non-hematological toxicity. This may include reducing the dose, withholding the drug until the toxicity is resolved, or discontinuing the drug all together. See the prescribing information for more detail.

**Other Uses with Supportive Evidence**

3. **Hodgkin Lymphoma.** Approve for 6 months if the patient meets the following criteria (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Bendamustine is used as second-line or subsequent therapy; AND
   C) Bendamustine is prescribed by or in consultation with an oncologist.

**Dosing.** Approve if the requested dosing meets the following criteria (A and B):
A) Each individual dose must not exceed 120 mg/m²; AND
B) The patient receives a maximum of two doses per 21-day or 28-day treatment cycle.

Three studies have assessed bendamustine in the treatment of relapsed or refractory Hodgkin lymphoma. These studies have utilized individual doses up to 120 mg/m² on two consecutive days of each cycle. Treatment cycles were 21 or 28 days in length and patients could receive up to 6 cycles of therapy.

Note: Dose modifications of bendamustine are recommended for the management of neutropenia, thrombocytopenia, and other non-hematological toxicity. This may include reducing the dose, withholding the drug until the toxicity is resolved, or discontinuing the drug all together. See the prescribing information for more detail.

4. **Multiple Myeloma.** Approve for 6 months if the patient meets the following criteria (A and B):
   A) The patient has relapsed or refractory disease; AND
   B) Bendamustine is prescribed by or in consultation with an oncologist.

**Dosing.** Approve if the requested dose meets the following criteria (A and B):
A) Each individual dose must not exceed 150 mg/m²; AND
B) The patient receives a maximum of two doses per 28-day cycle.
A number of studies have assessed bendamustine in the management of relapsed or refractory multiple myeloma.\textsuperscript{13-19} These studies have employed a range of doses, from 70 to 150 mg/m\textsuperscript{2} administered twice in each 28-day treatment cycle. Treatment duration varied across all of the studies and included 6 to 8 cycles in most studies,\textsuperscript{14,16-19} one study utilized six monthly induction cycles followed by six 2-month consolidation cycles,\textsuperscript{15} and one retrospective study treated patients until induction of remission or disease progression.\textsuperscript{13}

Note: Dose modifications of bendamustine are recommended for the management of neutropenia, thrombocytopenia, and other non-hematological toxicity.\textsuperscript{1-3} This may include reducing the dose, withholding the drug until the toxicity is resolved, or discontinuing the drug all together. See the prescribing information for more detail.

5. **T-Cell Lymphoma** (Note: Examples include Peripheral T-Cell Lymphoma, Mycosis Fungoides/Sezary Syndrome, Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders, Adult T-Cell Leukemia/Lymphoma, Hepatosplenic Gamma-Delta T-Cell Lymphoma).\textsuperscript{4,20,27} Approve for 6 months if bendamustine is prescribed by or in consultation with an oncologist.

**Dosing.** Approve if the requested dose meets the following criteria (A and B):

A) Each individual dose must not exceed 120 mg/m\textsuperscript{2}; AND

B) The patient receives a maximum of two doses in each 21-day cycle.\textsuperscript{21}

Note: Dose modifications of bendamustine are recommended for the management of neutropenia, thrombocytopenia, and other non-hematological toxicity.\textsuperscript{1-3} This may include reducing the dose, withholding the drug until the toxicity is resolved, or discontinuing the drug all together. See the prescribing information for more detail.

6. **Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma.** Approve for 6 months if bendamustine is prescribed by or in consultation with an oncologist.\textsuperscript{4,22}

**Dosing.** Approve if the requested dose meets the following criteria (A and B):

A) Each individual dose must not exceed 90 mg/m\textsuperscript{2}; AND

B) The patient receives a maximum of two doses in each 28-day cycle.\textsuperscript{23-25}

Limited dosing is available. Three studies employed a dose of 90 mg/m\textsuperscript{2} administered on Days 1 and 2 of a 28-day cycle in the treatment of Waldenstrom’s macroglobulinemia.\textsuperscript{23-25} Treatment continued for a maximum of 6 cycles.

Note: Dose modifications of bendamustine are recommended for the management of neutropenia, thrombocytopenia, and other non-hematological toxicity.\textsuperscript{1-3} This may include reducing the dose, withholding the drug until the toxicity is resolved, or discontinuing the drug all together. See the prescribing information for more detail.

**CONDITIONS NOT RECOMMENDED FOR APPROVAL**

Bendamustine has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).
1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

<table>
<thead>
<tr>
<th>Type of Revision</th>
<th>Summary of Changes</th>
<th>Approval Date</th>
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<tbody>
<tr>
<td>New policy</td>
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| Early annual revision | Added Balrapzo to the policy.  
Removed hematologist from criterion.  
Simplified Hodgkin Lymphoma criteria by removing information concerning combination therapy or use as a single agent.  
Revised Peripheral T-Cell Lymphoma indication to T-Cell Lymphoma and rolled Peripheral T-Cell Lymphoma, Mycosis Fungoides/Sezary Syndrome, Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders, Adult T-Cell Leukemia/Lymphoma, and Hepatosplenic Gamma-Delta T-Cell Lymphoma all under this indication.  
Removed use with rituximab or as a single agent from Waldenstrom Macroglobulinemia criteria.  
Removed Duration of Therapy and Note to Nurse Clinician from all criteria.  
Removed Other Cancer Related Indications                                                                                          | 07/17/2019    |