Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Bendamustine Agents (Bendeka®, Treanda®, Belrapzo®, Vivimusta®)	MP-RX-FP-10-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of Bendamustine agents *(Bendeka®, Treanda®, Belrapzo®, and Vivimusta®).* Bendamustine is an alkylating agent approved by the Food and Drug Administration (FDA) for the treatment of certain patients with blood cancers such as leukemias and lymphomas.

Background Information

Bendamustine is marketed under various brand names, including Belrapzo (Eagle Pharmaceuticals, Inc.), Bendeka (Teva Pharmaceuticals USA, Inc.), Treanda (Teva Pharmaceuticals USA, Inc.), and Vivmusta (Slayback Pharma LLC). It belongs to the class of mechlorethamine derivativesy, and these compounds have the ability to release electrophilic alkyl groups. These alkyl groups can form covalent bonds with electron-rich nucleophilic components, potentially leading to cell death through various pathways.

Bendamustine is effective against both quiescent (non-dividing) and dividing cells. Its alkylating activity, akin to nitrogen mustard, may involve the crosslinking of DNA single and double strands. Additionally, the benzimidazole ring in bendamustine may possess purine and amino acid antagonist properties, although the extent of its contribution to the drug's antitumor effects remains unclear. Despite these insights, the precise mechanism of action of bendamustine remains to be fully elucidated.

Treanda® (Teva Pharmaceuticals) received approval from the U.S. Food and Drug Administration (FDA) in March 2008 for CLL treatment and, in October 2008, for indolent B-cell NHL cases that have advanced despite previous treatment with rituximab or a rituximab-containing regimen. Its effectiveness compared to first-line CLL therapies (excluding chlorambucil) has not been determined.

Bendeka®, approved by the FDA in December 2015, was developed as a more convenient ready-to-dilute (RTD) formulation. It eliminates the need for reconstitution and can be administered directly as a pre-diluted solution, saving time and potentially reducing the risk of medication errors during preparation.

On May 15, 2018, the FDA granted approval to Belrapzo (Eagle Pharmaceuticals, Inc.), another ready-to-dilute (RTD) bendamustine hydrochloride (HCl) solution presented in a 500 mL admixture. This approval was granted for the treatment of patients diagnosed with chronic lymphocytic leukemia (CLL) and those with indolent B-cell non-Hodgkin lymphoma (NHL) that has advanced either during or within six months of receiving treatment with rituximab or a rituximab-containing regimen. Belrapzo® formulation eliminates the need for reconstitution and

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can be administered as a 500 mL admixture over either 30 or 60 minutes. The approval of Belrapzo was based on clinical studies previously conducted with Bendeka (Teva Pharmaceuticals USA, Inc.).

On December 7, 2022, the FDA approved Vivimusta® injection the treatment of chronic lymphocytic leukemia (CLL) and indolent B-cell non-Hodgkin lymphoma (NHL), following the 505(b)(2) pathway, with Belrapzo serving as the reference product.

The FDA approved indications for bendamustine include first line treatment of chronic lymphocytic leukemia (CLL) as well as indolent B-cell non-Hodgkin's lymphoma (NHL) that has progressed on treatment including rituximab. Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are different manifestations of the same disease and are managed in much the same way.

The National Comprehensive Cancer Network® (NCCN) provides additional recommendations with a category 2A level of evidence for the use of bendamustine. These recommendations include the use alone or in combination for previously treated multiple myeloma for relapse or progressive disease; as well as second-line, subsequent, or palliative therapy for classic Hodgkin lymphoma. NCCN also recommends bendamustine alone or in combination for primary, previously treated, progressive, or relapsed waldenstrom's macroglobulinemia. Bendamustine is recommended by NCCN for other types of non-Hodgkin's lymphoma (NHL) which is a group of blood cancers that includes all types of lymphoma except Hodgkin's lymphoma. NCCN recommends bendamustine in the following types of NHL:

- B-Cell lymphomas:
  - AIDS-related B-cell lymphoma
  - Diffuse large B-cell lymphoma
  - Follicular lymphoma
  - Gastric MALT lymphoma
  - High-Grade B-Cell Lymphomas
  - Mantle cell lymphoma
  - Nodal marginal zone lymphoma
  - Nongastric MALT lymphoma
  - Post-transplant lymphoproliferative disorders
  - Splenic marginal zone lymphoma

- T-Cell lymphomas:
  - Adult T-cell leukemia/lymphoma
  - Peripheral T-cell lymphomas
  - Breast Implant-associated Anaplastic Large Cell Lymphoma (ALCL)
  - Hepatosplenic T-cell lymphoma

As per the prescribing information, bendamustine products should not be administered to patients with a prior history of hypersensitivity reactions to bendamustine, which may include severe reactions like anaphylaxis and anaphylactoid responses. Bendamustine in its Belrapzo, Bendeka, and Vivimusta forms is also contraindicated

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for individuals with a known hypersensitivity to polyethylene glycol 400, propylene glycol, or monothioglycerol. Furthermore, Vivimusta should not be given to patients with a history of hypersensitivity to dehydrated alcohol.

According to the prescribing information, bendamustine (Belrapzo, Bendeka, Treanda, and Vivimusta) comes with the following warnings and precautions:

- Myelosuppression
- Infections
- Progressive multifocal leukoencephalopathy (PML)
- Anaphylaxis and infusion reactions
- Tumor lysis syndrome
- Skin reactions
- Hepatotoxicity
- Other malignancies
- Extravasation injury
- Embryo-fetal toxicity.

Definitions and Measures

- Multiple myeloma: A type of cancer that begins in plasma cells (white blood cells that produce antibodies).
- Non-Hodgkin Lymphoma (NHL): A heterogeneous group of lymphoproliferative disorders originating from B lymphocytes, T lymphocytes, or natural killer (NK) cells.
- Refractory Disease: Illness or disease that does not respond to treatment.
- Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.

Approved Indications

A. Chronic lymphocytic leukemia (CLL).
B. Indolent B-cell non-Hodgkin's lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

Other Uses

i. See Background section above.

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Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9036	Injection, bendamustine HCL (Belrapzo), 1mg (Effective 7/1/2019)
J9033	Injection, bendamustine HCL (Treanda), 1 mg
J9034	Injection, bendamustine HCL (Bendeka), 1 mg
J9056	Injection, bendamustine hydrochloride (vivimusta), 1 mg
J9058	Injection, bendamustine hydrochloride (apotex), 1 mg
J9059	Injection, bendamustine hydrochloride (baxter), 1 mg

ICD-10	Description
C81.10-C81.99	Classical/unspecified Hodgkin lymphoma
C82.00-C86.6	Non-Hodgkin lymphoma
C88.0	Waldenström's macroglobulinemia
C88.4	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma]
C90.00-C90.32	Multiple myeloma and malignant plasma cell neoplasms
C91.10-C91.12	Chronic lymphocytic leukemia of B-cell type
C91.50-C91.52	Adult T-cell lymphoma/leukemia (HTLV-1 associated)
E85.81	Light chain (AL) amyloidosis

Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Bendamustine agents (Bendeka®, Treanda®, Belrapzo®, and Vivimusta®)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

i. Individual has a diagnosis of one of the following:

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A. Chronic lymphocytic leukemia/small Lymphocytic lymphoma (CLL/SLL); **OR**
B. Relapsed, refractory or progressive classical Hodgkin lymphoma (NCCN 2A); **OR**
C. Non-Hodgkin lymphoma (NHL); **OR**
D. Relapsed, refractory or progressive Multiple myeloma (NCCN 2A); **OR**
E. Relapsed or refractory systemic light chain amyloidosis; **OR**
F. Waldenstrom's macroglobulinemia (NCCN 2A); **OR**
G. Cold agglutinin disease (DP BIIa; Jager 2020).

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Bendamustine agents (Bendeka®, Treanda®, Belrapzo®, and Vivimusta®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of unacceptable toxicity or disease progression while on the current regimen, and the maximum duration of therapy has not been exceeded. The following information should be submitted for reauthorization:
   A. A current oncology note documenting the patient's response to treatment showing no progression of disease.
   B. Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results.
ii. Maximum duration of treatment:
   A. Chronic Lymphocytic Leukemia (CLL): Up to 6 Cycles
   B. Non-Hodgkin Lymphoma (NHL): Up to 8 Cycles

C. Authorization Duration

i. Initial Approval Duration: Per Cycle
ii. Reauthorization Approval Duration: Per Cycle

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Treatment of metastatic breast cancer; **OR**
ii. Treatment of small cell lung cancer (SCLC); **OR**
iii. When the above criteria (Section A: Criteria for Initial Approval) are not met and for all other indications.
iv.

Limits or Restrictions

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A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Product	Use	Recommended Dosing Schedule	Recommended Treatment Duration
Bendeka®, Treanda®, Belrapzo®, Vivimusta®	Chronic Lymphocytic Leukemia (CLL)	100 mg/m2 i.v. on Days 1 and 2 of a 28-day cycle, up to 6 cycles.	6 Cycles
Bendeka®, Treanda®, Belrapzo®, Vivimusta®	Non-Hodgkin Lymphoma (NHL)	120 mg/m2 i.v. on Days 1 and 2 of a 21-day cycle, up to 8 cycles.	8 Cycles
Exceptions			
None			

Reference Information

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: January 3, 2023.
2. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
3. Jager U, Barcellini W, Broome C, et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the first International Consensus meeting. Blood Rev. 2020; 41:100648.
4. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2023; Updated periodically.
5. NCCN Clinical Practice Guidelines in Oncology™. © 2023 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed January 2023.
    a. Chronic Lymphocytic leukemia/small lymphocytic lymphoma. V1.2023. Revised August 30, 2022.
    b. B-Cell Lymphomas. V5.2022. Revised July 12, 2022.
    c. T-Cell Lymphomas. V2.2022. Revised March 7, 2022.
    d. Waldenstrom Macroglobulinemia/Lymphoplasmacytic lymphoma. V1.2023. Revised July 6, 2022.
    e. Multiple Myeloma. V3.2023. Revised December 8, 2022.
    f. Hodgkin Lymphoma. V2.2023. Revised November 8, 2022.
    g. Pediatric Hodgkin Lymphoma. V1.2022. Revised April 8, 2022.

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h. Systemic Light Chain Amyloidosis. V2.2023. Revised November 28, 2022.
i. Hematopoietic Cell Transplantation (HCT). V2.2022. Revised September 28, 2022.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	MPCC Approval Date
Annual Review 11/12/2024	Clarify criteria to include progressive Hodgkin lymphoma and refractory multiple myeloma per NCCN. Minor formatting changes. Coding Reviewed: No changes.	2/18/2025	3/6/2025
Select Review 2/15/2024	Update statement for criteria for initial approval: Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met all approval criteria.	3/25/2024	5/9/2024
Policy Inception 11/12/2024	Elevance Health's Medical Policy adoption.	N/A	11/30/2023