CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL ONCOLOGY

Bendamustine Hydrochloride (Belrapzo®, Bendeka®, Treanda®, Vivimusta®)

Version: 1.0

EFFECTIVE DATE: 1/1/2024

NantHealth® | Eviti®

Please note the following:

Bendamustine Hydrochloride (Belrapzo®, Bendeka®, Treanda®, Vivimusta®)

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within 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.

Bendamustine hydrochloride (Belrapzo, Bendeka, Treanda, Vivimusta): Discussion

Bendamustine is a chemotherapeutic agent that displays a unique pattern of cytotoxicity designed to have both alkylating and antimetabolite properties. Molecular analyses have revealed that bendamustine differs from other alkylating agents in its mechanism of action. Differences have been observed regarding its effects on DNA repair and cell cycle progression. Moreover, bendamustine can induce cell death through both apoptotic and nonapoptotic pathways, thereby retaining activity even in cells without a functional apoptotic pathway. Bendamustine has demonstrated significant efficacy in patients with indolent lymphomas and chronic lymphocytic leukemia (CLL), including in patients with disease refractory to conventional alkylating agents and rituximab.[1]

Bendamustine hydrochloride is approved by the Food and Drug Administration (FDA) for the treatment of:

1. Adult patients with chronic lymphocytic leukemia.
2. Adult patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.[2,3,4,5,6]

The National Comprehensive Cancer Network (NCCN) endorses bendamustine hydrochloride in the following cancer types: B-cell lymphomas, chronic lymphocytic leukemia/small lymphocytic lymphoma, hematopoietic cell transplantation, Hodgkin lymphoma, multiple myeloma, pediatric Hodgkin lymphoma, small cell lung cancer, systemic light chain amyloidosis, T-cell lymphomas, and Waldenström macroglobulinemia/lymphoplasmacytic lymphoma. [7,8,9,10,11,12,13,14,15,16]

Bendamustine hydrochloride: Definitions

- **Apoptosis-** A type of cell death in which a series of molecular steps in a cell lead to its death. This is one method the body uses to remove unneeded or abnormal cells. The process of apoptosis may be blocked in cancer cells, also called programmed cell death.

- **Bing-Neel Syndrome -** A rare manifestation of Waldenström's macroglobulinemia where malignant lymphoplasmacytic cells infiltrate the central nervous system (CNS).
- **del(17p)/TP53 mutation** - The loss of all or part of the short arm (also called the p arm) of chromosome 17. The deletion 17p leads to the loss of the tumor suppressor gene TP53. Mutations (changes) in the TP53 gene may cause cancer cells to grow and spread in the body.
- **Food and Drug Administration (FDA)** – The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- **Indolent lymphoma -** A type of lymphoma that tends to grow and spread slowly and has few symptoms. Also called low-grade lymphoma
- **National Comprehensive Cancer Network (NCCN) -** An alliance of thirty-two leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.
- **TP53 mutation** - A gene that makes a protein that is found inside the nucleus of cells and plays a key role in controlling cell division and cell death. Mutations (changes) in the TP53 gene may cause cancer cells to grow and spread in the body.
- **Stage I_1 -** Disease of the mucosa and submucosa that is confined to the GI tract.
- **Stage I_2 -** Disease of the muscularis propria and serosa that is confined to the GI tract.
- **Stage II_1 -** Disease that has local nodal involvement that extends into the abdomen.
- **Stage II_E -** Disease with penetration of the serosa to the involved adjacent organs or tissues.

Bendamustine Hydrochloride: Policy

Bendamustine Hydrochloride will be considered for coverage when the following criteria are met:

B-Cell Lymphomas

Diffuse Large B-Cell Lymphoma (DLBCL, High-Grade B-Cell)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Second-line and subsequent therapy in combination with polatuzumab vedotin-piiq with or without rituximab if there is no intention to proceed to transplant for one of the following:
   a) Relapsed or refractory disease > 12 months after completion of first-line therapy
   b) Primary refractory disease (partial response, no response, or progression) OR relapsed disease < 12 months after completion of first-line therapy if no intention to proceed to CAR-T cell therapy
   c) Alternative systemic therapy (if not previously used) for relapsed/refractory disease if no intention to proceed to CAR-T cell therapy.

Note: Used as clinically indicated as a bridging option (consider/add bendamustine only after leukapheresis) in combination with polatuzumab vedotin-piiq, and with or without rituximab until CAR T-cell product is available for primary refractory disease or relapsed disease < 12 months after completion of first-line therapy. [7]

Extranodal Marginal Zone Lymphoma of Non-gastric Sites (Noncutaneous)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. First-line therapy in combination with rituximab for stage IV disease or for recurrent stage IE or contiguous stage IIE disease; OR
4. Second-line and subsequent therapy in combination with rituximab or obinutuzumab (not recommended if previously treated with bendamustine) for relapsed, refractory, or progressive disease. [7]

Extranodal Marginal Zone Lymphoma of the Stomach [7]

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. In combination with rituximab for one of the following:
    a) First-line therapy for stage II_1 (distant nodal involvement that extends into the abdomen), or stage II_E (penetration of serosa to involved adjacent organs or tissues), or stage IV disease (distant nodal, advanced stage)
    b) Additional therapy for stage I_1 (mucosa or submucosa confined to the GI tract), or Stage I_2 (muscularis propria, serosa confined to the GI tract), or stage II_1 (local nodal involvement that extends into the abdomen) with H. pylori-positive disease if repeat endoscopy shows no response or recurrence after antibiotic therapy and involved site radiation therapy (ISRT)
    c) Additional therapy after ISRT or rituximab alone for stage I_1 (mucosa or submucosa confined to the GI tract), or stage I_2 (muscularis propria, serosa confined to the GI tract), or stage II_1 (local nodal involvement that extends into the abdomen) disease that is lymphoma positive after restaging with endoscopy; OR

4. Second-line and subsequent therapy for relapsed, refractory, or progressive disease in combination with rituximab or obinutuzumab (not recommended if previously treated with bendamustine). [7]

Follicular Lymphoma (Grade 1-2)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. First-line therapy in combination with rituximab or obinutuzumab for stage I, contiguous stage II, non-contiguous stage II disease, or stage III or IV disease; OR
4. Second-line and subsequent therapy (if not previously given) in combination with rituximab or obinutuzumab for no response, relapsed, or progressive disease; OR

5. Second-line and subsequent therapy (if not previously given) in combination with polatuzumab vedotin-piiq with or without rituximab for no response, relapsed, or progressive disease. [7]

Note: Obinutuzumab is preferred in rituximab refractory patients, which includes disease progressing on or within 6 months of prior rituximab therapy.

Histologic Transformation of Indolent Lymphomas to Diffuse Large B-Cell Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. In combination with polatuzumab vedotin-piiq with or without rituximab if previously treated with an anthracycline-based regimen and no intention to proceed to transplant as an additional therapy for partial response, no response, or progressive disease following chemoimmunotherapy if the histologic transformation to diffuse large B-cell lymphoma after minimal or no prior treatment, OR after multiple lines of chemoimmunotherapy for indolent or transformed disease. [7]

HIV-Related B-Cell Lymphomas

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Second-line and subsequent therapy in combination with polatuzumab vedotin-piiq with or without rituximab for HIV-related diffuse large B-cell lymphoma, primary effusion lymphoma, and HHV8-positive diffuse large B-cell lymphoma, not otherwise specified, or without rituximab for relapse of plasmablastic lymphoma if there is no intention to proceed to transplant for one of the following:
   a) Relapsed or refractory disease >12 months after completion of first-line therapy
   b) Primary refractory disease (partial response, no response, or progression) or relapsed disease < 12 months after completion of first-line therapy if no intention to proceed to CAR-T cell therapy
   c) Alternative systemic therapy (if not previously used) for relapsed/refractory disease if no intention to proceed to CAR-T cell therapy.

Note: Used as clinically indicated as a bridging option (consider/add bendamustine only after leukapheresis) in combination with polatuzumab vedotin-piiq and with or without rituximab until CAR-T cell product is available for primary refractory disease or relapsed disease < 12 months after completion of first-line therapy. [7]

Mantle Cell Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Less aggressive induction therapy used in combination with rituximab OR as a component of RBAC500 (rituximab, bendamustine, and cytarabine) regimen for one of the following:
   a) Stage I-II disease as initial therapy

b) As an additional therapy for partial response, progression, or relapse after initial treatment with involved site radiation therapy (ISRT) alone
c) As re-induction therapy, in selected cases, for relapse after initial treatment with chemoimmunotherapy
d) For classical or indolent TP53 wildtype stage II bulky or noncontiguous, III, or IV disease if not suitable for aggressive induction therapy; OR

4. In the absence of a clinical trial, and if not suitable for aggressive therapy, consider as less aggressive induction therapy in combination with rituximab OR as a component of RBAC500 (rituximab, bendamustine, and cytarabine) regimen for classical or indolent TP53 mutated stage II bulky or noncontiguous, III, or IV disease; OR

Note: TP53 mutation has been associated with poor prognosis in patients treated with conventional therapy, including transplant-clinical trial is strongly recommended.

5. Aggressive induction therapy in combination with rituximab followed by rituximab in combination with high-dose cytarabine for one of the following:
    a) As an additional therapy for stage I-II disease following partial response, progression, or relapse after initial treatment with involved site radiation therapy (ISRT) alone
    b) As re-induction therapy, in selected cases, for relapse after initial treatment with chemoimmunotherapy
    c) For classical or indolent TP53 wildtype stage II bulky or noncontiguous, III, or IV disease; OR

6. Useful in certain circumstances as second-line and subsequent therapy (not recommended if previously treated with bendamustine) in combination with rituximab OR as a component of RBAC500 (rituximab, bendamustine, and cytarabine) regimen for one of the following:
    a) Stage I-II disease with partial response, progression, or relapse after prior treatment with chemoimmunotherapy
    b) Classical or indolent stage II bulky or noncontiguous, III, or IV disease in patients who have stable or progressive disease, or partial response with substantial disease after induction therapy
    c) Relapsed or refractory disease

Note: Bendamustine should be used with caution in patients intended to receive high-dose therapy/autologous stem cell rescue, as there is conflicting data regarding the ability to collect peripheral progenitor cells. [7]

Nodal Marginal Zone Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. First-line therapy in combination with rituximab or obinutuzumab for stage I, contiguous stage II, non-contiguous stage II, or stage III, IV disease; OR
4. Second-line and subsequent therapy in combination with rituximab or obinutuzumab (not recommended if previously treated with bendamustine) for relapsed, refractory, or progressive disease. [7]

Post-Transplant Lymphoproliferative Disorders (PTLD)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Second-line and subsequent therapy in patients with monomorphic PTLD (B-cell type) for one of the following:
    a) For relapsed or refractory disease > 12 months after completion of initial treatment with chemoimmunotherapy
    b) For primary refractory disease (partial response, no response, or progression) or relapsed disease <12 months after completion of initial treatment with chemoimmunotherapy if no intention to proceed to CAR-T cell therapy
    c) As alternative systemic therapy (if not previously used) for relapsed/refractory disease if no intention to proceed to CAR-T cell therapy.

Note:

1. Used if this is no intention to proceed to transplant in combination with polatuzumab vedotin-piiq and with or without rituximab.

2. Used as clinically indicated as a bridging option (consider/add bendamustine only after leukapheresis) in combination with polatuzumab vedotin-piiq and with or without rituximab until CAR T-cell product is available for primary refractory disease or relapsed disease <12 months after completion of initial treatment with chemoimmunotherapy. [7]

Splenic Marginal Zone Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. First-line therapy in combination with rituximab for disease recurrence following initial management of splenomegaly in treatment naïve patients; OR
4. In combination with rituximab or obinutuzumab for disease recurrence following initial management of splenomegaly as second-line therapy (if previously treated with rituximab) and subsequent therapy (not recommended if previously treated with bendamustine). [7]

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. First-line therapy in combination with rituximab or obinutuzumab without del(17p)/TP53 mutation (not recommended for frail patients); OR
4. Subsequent therapy in combination with rituximab (if not given as first-line) for CLL/SLL without del(17p)/TP53 mutation for relapsed or refractory disease after prior Bruton Tyrosine Kinase inhibitor- and venetoclax-based regimens (not recommended for frail patients). [8]

Hematopoietic Cell Transplantation

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Conditioning for autologous transplant in combination with etoposide, cytarabine, and melphalan for Non-Hodgkin Lymphoma without CNS disease or Hodgkin Lymphoma [9]

Hodgkin Lymphoma

1. Age 18 years or older; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Second-line or subsequent systemic therapy (if not previously used) in combination with brentuximab vedotin, OR as a component of gemcitabine/bendamustine/vinorelbine for relapsed or refractory disease; OR
4. Therapy for disease refractory to at least 3 prior lines of therapy as a single agent, OR in combination with carboplatin and etoposide; OR
5. Palliative therapy as a single agent for relapsed or refractory disease in patients older than 60 years of age; OR
6. Second-line or subsequent systemic therapy (if not previously used) for progressive, relapsed, or refractory nodular lymphocyte-predominant Hodgkin Lymphoma as a component of bendamustine + rituximab. [10]

Multiple Myeloma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Therapy for previously treated disease for late relapse or progressive disease (>3 prior therapies) in combination with one of the following:
   a) Lenalidomide and dexamethasone
   b) Bortezomib and dexamethasone
   c) Carfilzomib and dexamethasone
   d) As a single agent [11]

Pediatric Classical Hodgkin Lymphoma

1. Less than or equal to 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Re-induction therapy or subsequent therapy (if not previously used), in combination with brentuximab vedotin, for relapsed or refractory disease as a consideration in patients with heavily pretreated disease (with platinum or anthracycline-based chemotherapy) or if a decrease in cardiac function observed; OR
4. Re-induction therapy in combination with brentuximab vedotin and involved site radiation therapy (ISRT) for relapsed or refractory disease (only in highly favorable patients) as a consideration in patients with heavily pretreated disease (with platinum or anthracycline-based chemotherapy) or if a decrease in cardiac function observed

Note: Recommended for those who may avoid autologous stem cell rescue (ASCR):

initial stage other than IIIB or IVB, no prior exposure to radiation therapy (RT), duration of first complete response (CR1) > 1 year, absence of extranodal disease or B symptoms at relapse. [12]

Small Cell Lung Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Subsequent systemic therapy for patients with performance status 0-2 as a single agent for relapse following complete or partial response or stable disease with primary treatment OR primary progressive disease. [13]

Systemic Light Chain Amyloidosis

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Treatment for relapsed/refractory disease in combination with dexamethasone. [14]

T- Cell Lymphomas

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Second-line or subsequent therapy as a single agent for non-responders to first-line therapy for acute or lymphoma subtypes

Breast Implant-Associated ALCL

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Second-line and subsequent therapy for relapsed/refractory disease, as a single agent

Hepatosplenic T-Cell Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Single agent for refractory disease after 2 first-line therapy regimens

Peripheral T-Cell Lymphomas

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. As a single agent as initial palliative intent therapy or second-line and subsequent therapy for relapsed/refractory for one of the following:
    a) Anaplastic large cell lymphoma (ALCL)
    b) Angioimmunoblastic T-cell lymphoma (AITL)
    c) Enteropathy-associated T-cell lymphoma (EATL)
    d) Follicular T-cell lymphoma (FTCL)

e) Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)
f) Nodal peripheral T-cell lymphoma with TFH phenotype (PTCL, TFH)
g) Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS)[15]

Waldenström Macroglobulinemia

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Used as primary therapy or consider for relapse if previously used as primary therapy that was well tolerated and elicited a prolonged response, or as an alternative therapy for previously treated disease with persistent symptoms following primary therapy or that does not respond to primary therapy or for progressive or relapsed disease in combination with rituximab OR as a single agent; OR
4. Used for the management of symptomatic Bing-Neel syndrome as a single agent OR in combination with rituximab if systemic control is needed. [16]

Note: Coverage of bendamustine hydrochloride will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation OR when all criteria are met.

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Bendamustine Hydrochloride: References

1. Bendamustine: mechanism of action and clinical data. https://pubmed.ncbi.nlm.nih.gov/22362008. Accessed May 18, 2023.
2. Bendamustine Hydrochloride Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215033s000lbl.pdf. Accessed May 18, 2023.
3. Bendamustine Hydrochloride (Belrapzo®) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/205580s010lbl.pdf. Accessed May 18, 2023.
4. Bendamustine Hydrochloride (Bendeka®) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208194s024lbl.pdf. Accessed May 18, 2023.
5. Bendamustine Hydrochloride (Treanda®) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022249s026lbl.pdf. Accessed May 18, 2023.
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7. National Comprehensive Cancer Network Guidelines. B-Cell Lymphomas (Version 3.2023). https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed May 18, 2023.
8. National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed May 19, 2023.
9. National Comprehensive Cancer Network. Hematopoietic Cell Transplantation (HCT) (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/hct.pdf. Accessed May 19, 2023.
10. National Comprehensive Cancer Network. Hodgkin Lymphoma (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf. Accessed May 19, 2023.
11. National Comprehensive Cancer Network. Multiple Myeloma (Version 3.2023). https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed May 19, 2023.
12. National Comprehensive Cancer Network. Pediatric Hodgkin Lymphoma (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/ped_hodgkin.pdf. Accessed June 1, 2023.
13. National Comprehensive Cancer Network. Small Cell Lung Cancer (Version 3.2023). https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. Accessed May 22, 2023.
14. National Comprehensive Cancer Network. Systemic Light Chain Amyloidosis (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/amyloidosis.pdf. Accessed May 22, 2023.
15. National Comprehensive Cancer Network. T-Cell Lymphomas (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf. Accessed May 22, 2023.
16. National Comprehensive Cancer Network. Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf. Accessed May 23, 2023.

Bendamustine Hydrochloride: Coding (CPT®, ICD 10 and HCPCS) *

*Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

CODE	DESCRIPTION
C34.9-C34.92	Small Cell Lung Cancer
C81.10-C81.99	Classic Hodgkin Lymphoma
C81. 90	Pediatric Hodgkin Lymphoma
C82.00-C86.6	Non-Hodgkin lymphoma
C90.00-C90.32	Multiple Myeloma

C91.10, C91.12	Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
C84.40-C84.49, C84.60-C84.69, C84.70-C84.79, C86.2, C86.5, C91.50, C91.52	T-Cell Lymphomas
C88.0	Waldenström Macroglobulinemia
C9399	Unclassified Drug or Biologicals
E85.81	Systemic Light Chain Amyloidosis
Z94.81, Z94.89, Z94.9	Hematopoietic Cell Transplantation
J9033	Bendamustine HCL (Treanda®)
J9034	Bendamustine HCL (Bendeka®)
J9036	Bendamustine HCL (Belrapzo®)
J9999	Bendamustine HCL (Vivimusta®) (No CODE in drug feed. CMS has a code J9056)

Bendamustine Hydrochloride: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2024
2	Policy Review Dates:	6/12/2023
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee Approval Dates:	7/17/2023
6	Revision Changes:	