# Clinical Policy: Bendamustine (Belrapzo, Bendeka, Treanda, Vivimusta)

Reference Number: PA.CP.PHAR.307
Effective Date: 01/2018
Last Review Date: 10/2024

**Description**
Bendamustine hydrochloride (Belrapzo®, Bendeka®, Treanda®, Vivimusta™) is an alkylating drug.

**FDA Approved Indication(s)**
Belrapzo, Bendeka, Treanda, and Vivimusta are indicated for the treatment of patients with:

- Chronic lymphocytic leukemia (CLL); Efficacy relative to first line therapies other than chlorambucil has not been established
- Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen

**Policy/Criteria**
It is the policy of PA Health & Wellness ® that Belrapzo, Bendeka, Treanda, Vivimusta and bendamustine are 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. Prescribed in combination with rituximab or Gazyva®;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 100 mg/m$^2$ on Days 1 and 2 of a 28-day cycle, up to 6 cycles;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Approval duration: 6 months**

**B. Non-Hodgkin B-Cell Lymphomas** (must meet all)**:**

1. One of the following diagnoses (a-h):
   a. Indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen;
   b. Classic follicular lymphoma;
   c. Marginal zone lymphoma (MZL) (i, ii or ii):
      i. Splenic MZL;
      ii. Nodal MZL
      iii. Extranodal mucosa-associated lymphoid tissues (MALT) (1 or 2):
         1) Gastric MALT lymphoma;
         2) Nongastric MALT lymphoma;
   d. Mantle cell lymphoma;

e. Diffuse large B-cell lymphoma(DLBCL) with no intention to proceed to transplant (*as subsequent therapy*);*
f. HIV-related B-cell lymphoma (*as subsequent therapy*);*
g. Monomorphic post-transplant lymphoproliferative disorder (PTLD) (B-cell type) (*as subsequent therapy*);*
h. High-grade B-cell lymphomas;

**See Appendix B - prior authorization may be required for prior therapies*

2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. For classical follicular lymphoma, MZL: prescribed in combination with rituximab or Gazyva;
5. For mantle cell lymphoma, prescribed in combination with rituximab;
6. For indolent B-cell non-Hodgkin lymphoma, DLBCL, HIV-related B-cell lymphoma, PTLD, high-grade B-cell lymphomas: prescribed in combination with Polivy® with or without rituximab;
7. Request meets one of the following (a or b):
   a. Dose does not exceed 120 mg/m$^2$ on Days 1 and 2 of a 21-day cycle, up to 8 cycles;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Approval duration: 6 months**

**C. NCCN Recommended Uses (off-label)** (must meet all)**:**

1. Diagnosis of one of the following (a-h):
   a. Hodgkin lymphoma (HL),as subsequent therapy;*
   b. Pediatric HL that is relapsed or refractory, as re-induction or subsequent therapy;*
   c. Hematopoietic cell transplantation for NHL without central nervous system (CNS) disease or for HL;
   d. Multiple myeloma (MM) that is relapsed or refractory, as subsequent therapy after 3 prior therapies;*
   e. Mycosis fungidoes (MF)/Sezary Syndrome (SS);
   f. One of the following T-cell lymphomas (i, ii, iii or iv):
      i. Adult T-cell leukemia/lymphoma (ATLL), as subsequent therapy;*
      ii. Hepatosplenic T-cell lymphoma (HSTCL), as subsequent therapy;*
      iii. Breast implant-associated ALCL, as subsequent therapy;*
      iv. One of the following peripheral T-cell lymphoma (PTCL) subtypes, as initial palliative intent therapy or subsequent treatment therapy (1-7):
         1) Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS);
         2) Angioimmunoblastic T-cell lymphoma (AITL),
         3) Anaplastic large cell lymphoma (ALCL);
         4) Enteropathy-associated T-cell lymphoma (EATL),
         5) Follicular T-cell (TFH) lymphoma;
         6) Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL),
         7) Nodal PTCL with TFH phenotype;
   g. Systemic light chain amyloidosis (SLCA) that is relapsed/refractory;

h. Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma (including management of Bing–Neel syndrome);

**See Appendix B - prior authorization may be required for prior therapies*

2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years, unless diagnosis is pediatric HL;
4. For hematopoietic cell transplantation, prescribed in combination with etoposide, cytarabine, and melphalan;
5. For MF/SS: prescribed in combination with Adcentris;
6. For T-cell lymphomas: prescribed as a single agent or in combination with Adcentris®;
7. For SLCA: prescribed in combination with dexamethasone;
8. For Waldenstrom's macroglobulinemia: prescribed as a single agent or in combination with rituximab;
9. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Approval duration: 6 months**

**B. 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): PA.CP.PMN.53

## II. Continued Approval

**A. All Indications in Section I** (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.PHARM.01) applies;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets (a or b):
   a. New dose does not exceed (i or ii):
      i. CLL/SLL: 100 mg/m$^2$ on Days 1 and 2 of a 28-day cycle, up to 6 cycles;
      ii. Non-Hodgkin indolent B-cell lymphoma: 120 mg/m$^2$ on Days 1 and 2 of a 21-day cycle, up to 8 cycles;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Approval duration: 12 months**

**B. Other diagnoses/indications** (must meet 1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.PHARM.01) applies; or
2. Refer to PA.CP.PMN.53

**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 – PA.CP.PMN.53 for Medicaid or evidence of coverage documents.

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

AITL: angioimmunoblastic T-cell lymphoma
ALCL: anaplastic large cell lymphoma
ATLL: adult T-cell leukemia/lymphoma
CLL: chronic lymphocytic leukemia
CNS: central nervous system
DLBCL: diffuse large B-cell lymphoma
EATL: enteropathy-associated T-cell lymphoma
FDA: Food and Drug Administration
HIV: human immunodeficiency virus
HL: Hodgkin lymphoma
HSTCL: hepatosplenic gamma-delta T-cell lymphoma
MF: mycosis fungoides
MALT: mucosa-associated lymphoid tissue
MEITL: monomorphic epitheliotropic intestinal T-cell lymphoma
MM: multiple myeloma
MCL: marginal zone lymphoma
NCCN: National Comprehensive Cancer Network
NHL: non-Hodgkin lymphoma
PTCL: peripheral T-cell lymphoma
PTLD: post-transplant lymphoproliferative disorder
PTLD-NOS: post-transplant lymphoproliferative disorder not otherwise specified
SLCA: systemic light chain amyloidosis
SLL: small lymphocytic lymphoma
SS: Sezary syndrome
TFH: follicular T-cell

*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 and may require prior authorization.*

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| **Examples of primary therapies (NCCN)** | | |
| **B-cell NHL (e.g. DLBCL, HIV-related B-cell lymphoma, PTCL)** | | |
| RCHOP<br>Rituxan® (rituximab) + cyclophosphamide, doxorubicin, vincristine, prednisone) | Varies | Varies |
| EPOCH<br>(etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + Rituxan® (rituximab) | Varies | Varies |
| RCDOP Rituxan® (rituximab) + (cyclophosphamide, liposomal doxorubicin, vincristine, prednisone) | Varies | Varies |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| RCEOP Rituxan® (rituximab) + (cyclophosphamide, etoposide, vincristine, prednisone) | Varies | Varies |
| RGCVP Rituxan® (rituximab) + (gemcitabine, cyclophosphamide, vincristine, prednisone) | Varies | Varies |
| RCEPP Rituxan® (rituximab) + (cyclophosphamide, etoposide, prednisone, procarbazine) | Varies | Varies |
| Pola-R-CHP (Polivy [polatuzumab vedotin-piiq], Rituxan [rituximab], cyclophosphamide, doxorubicin, prednisone) | Varies | Varies |
| **HL** | | |
| ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) + Rituxan (rituximab) | Varies | Varies |
| RCHOP Rituxan (rituximab) + (cyclophosphamide, doxorubicin, vincristine, prednisone) | Varies | Varies |
| CVbp (cyclophosphamide, vinblastine, prednisolone) + Rituxan (rituximab) | Varies | Varies |
| Rituxan (rituximab) | Varies | Varies |
| **MM** | | |
| Bortezomib/lenalidomide/dexamethasone | Varies | Varies |
| Carfilzomib/lenalidomide/dexamethasone | Varies | Varies |
| Daratumumab/lenalidomide/dexamethasone | Varies | Varies |
| **T-cell Lymphomas (e.g. HSTCL, ATLL)** | | |
| ICE (ifosfamide, carboplatin, etoposide) | Varies | Varies |
| DHAP (dexamethasone, andcisplatin, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) | Varies | Varies |
| EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + Rituxan (rituximab) | Varies | Varies |
| HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine | Varies | Varies |
| CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone) | Varies | Varies |
| CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) | Varies | Varies |
| Polivy (brentuximab vedotin) ± CHP (cyclophosmaide, doxorubicin, prednisone) | Varies | Varies |

*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):

  - Belrapzo, Bendeka: patients with a history of a hypersensitivity reaction to bendamustine, polyethylene glycol 400, propylene glycol, or monothioglycerol
  - Treanda: patients with a history of a hypersensitivity reaction to bendamustine
  - Vivimusta: patients with a history of a hypersensitivity reaction to bendamustine, polyethylene glycol 400, dehydrated alcohol, or monothioglycerol
- Boxed warning(s): none reported

## V. Dosage and Administration

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| CLL/SLL* | Bendeka: 100 mg/m$^2$ IV over 10 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles<br><br>Belrapzo, Treanda: 100 mg/m$^2$ IV over 30 minutes on days 1 and 2 of a 28-day cycle, up to 6 cycles<br><br>Vivimusta: 100 mg/m$^2$ IV over 20 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles | See regimen |
| Indolent B-cell lymphoma* | Bendeka: 120 mg/m$^2$ IV over 10 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles<br><br>Belrapzo, Treanda: 120 mg/m$^2$ IV over 60 minutes on days 1 and 2 of a 21-day cycle, up to 8 cycles<br><br>Vivimusta: 120 mg/m$^2$ IV over 20 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles | See regimen |

**Non-Hodgkin lymphomas*

## VI. Product Availability

| Drug Name | Availability |
|---|---|
| Bendamustine (Belrapzo, Bendeka, Vivimusta) | Solution (multiple-dose vial): 100 mg/4 mL |
| Bendamustine (Treanda) | Lyophilized powder (single-dose vial): 25 mg in a 20 mL vial; 100 mg in a 20 mL vial |

## VII. References

1. Belrapzo Prescribing Information. Woodcliff Lake, NJ: Eagle Pharmaceuticals, Inc; January2024. Available at: www.belrapzo.com. Accessed August 6, 2024.
2. Bendeka Prescribing Information. Parsippany, NJ: Teva Pharmaceuticals; January 2024. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/208194s026lbl.pdf.. Accessed August 10, 2023

3. Treanda Prescribing Information. Parsippany, NJ: Teva Pharmaceuticals; October 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022249s026lbl.pdf. Accessed August 6, 2024.
4. Vivimusta Prescribing Information. Princeton, NJ: Slayback Pharma; December 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212209s005lbl.pdf.Accessed August 6, 2024.
5. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. August 6, 2024.
6. National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 3.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. August 6, 2024.
7. National Comprehensive Cancer Network. B-cell Lymphomas Version 2.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. August 6, 2024.
8. National Comprehensive Cancer Network. Hodgkin Lymphoma Version 3.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf. August 6, 2024.
9. National Comprehensive Cancer Network. Multiple Myeloma Version 4.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. August 6, 2024.
10. National Comprehensive Cancer Network. T-cell Lymphomas Version 4.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf. August 6, 2024.
11. National Comprehensive Cancer Network. Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma Version 2.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf. August 6, 2024.

**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.

| HCPCS Codes | Description |
|---|---|
| J9033 | Injection, bendamustine HCl (Treanda), 1 mg |
| J9034 | Injection, bendamustine HCl (Bendeka), 1 mg |
| J9036 | Injection, bendamustine HCl, (Belrapzo), 1 mg |
| J9056 | Injection, bendamustine hydrochloride (vivimusta), 1 mg |
| J9058 | Injection, bendamustine hydrochloride (apotex), 1 mg |
| J9059 | Injection, bendamustine hydrochloride (baxter), 1 mg |

| Reviews, Revisions, and Approvals | Date |
|---|---|
| 4Q 2018 annual review: summarized NCCN and FDA-approved uses for improved clarity; added specialist involvement in care; added PTLD (category 2A recommendation) as a covered indication per NCCN compendium; updated continued therapy section to include language for continuity of care; references reviewed and updated. | 07/2018 |
| 4Q 2019 annual review: No changes per Statewide PDL implementation 01-01-2020 | 10/2019 |

| HCPCS Codes | Description | |
|---|---|---|
| | 4Q 2020 annual review: off-label criteria sets combined into one - additional criteria limited to subsequent therapy requirement; added additional therapeutic alternatives to Appendix B with NCCN category 1: MM; added hepatosplenic gamma-delta T-cell lymphoma to non-Hodgkin T-cell lymphomas (off-label) uses and related therapeutic alternatives to Appendix B; appendix B prior therapy examples truncated; references reviewed and updated. | 10/2020 |
| | 4Q 2021 annual review: added Belrapzo; per NCCN category 2A recommendations: added requirements for combination use for CLL, MALT lymphoma, and marginal zone lymphoma; clarified types of PTCLs; removed gamma delta requirement from HSTCL; added off-label indications of breast-implant ALCL, nodular lymphocyte-predominant HL, pediatric HL, and high-grade B-cell lymphomas; for off-label indications, revised age requirement to allow bypass if diagnosis is pediatric HL; references reviewed and updated. | 10/2021 |
| | 4Q 2022 annual review: added SLCA and hematopoietic cell transplantation under NCCN recommended use given category 2A recommendation; removed primary cutaneous lymphomas as use is no longer supported by NCCN primary cutaneous lymphoma guideline; references reviewed and updated. | 10/2022 |
| | RT4: added new dosage form Vivimusta | 01/2023 |
| | 4Q 2023 annual review: removed combination use with Arzerra for CLL from initial criteria as use is no longer supported by NCCN CLL/SLL guideline; renamed AIDS-related B-cell lymphoma to HIV-related per NCCN naming changes; references reviewed and updated. | 11/2023 |
| | 4Q 2024 annual review: clarified that policy applies to generic bendamustine; for all indications, revised commercial approval duration to “6 months or to the member’s renewal date, whichever is longer”; for NHL per NCCN, clarified follicular lymphoma is classic, updated formatting for MZL to clarify types; specified DLBL is with no intention to proceed to transplant, revised high-grade B-cell lymphoma criteria to lymphoma with no intention to proceed to transplant, added requirements for combination use for classic follicular lymphoma, MZL, indolent NHL, DLBCL, HIV-related B-cell lymphoma, PTLD, and high-grade B-cell lymphoma per NCCN; for off-label NCCN uses per NCCN, added relapsed or refractory requirements to HL, MM, and SLCA, added as subsequent therapy requirement to MM and PTCL, added initial therapy requirement to PTCL; added off-label indications of MF/SS, EATL, and ALCL, clarified PTCL subtypes, clarified Waldenstrom’s macroglobulinemia includes Bing-Neel syndrome, added requirements for combination use for T-cell lymphomas, MF/SS, and Waldenstrom’s macroglobulinemia; updated Appendix B per NCCN; removed bendamustine 45mg and 180mg vials per product discontinuation; removed inactive HCPCS codes; references reviewed and updated. | 10/2024 |