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

Reference Number: CP.PHAR.307
Effective Date: 02.01.17
Last Review Date: 11.22
Line of Business: Commercial, HIM*, Medicaid

Coding Implications
Revision Log

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

Description

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

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***For Health Insurance Marketplace (HIM),** if request is through pharmacy benefit, generic bendamustine is non-formulary and should not be approved using these criteria; refer to the formulary exception policy, HIM.PA.103.*

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

Provider must submit documentation (such as office chart notes and 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 Belrapzo, Bendeka, Treanda, and Vivimusta 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 chronic lymphocytic leukemia (CLL) (i.e., 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, Arzerra®, 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*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Commercial/Medicaid – 6 months
HIM – 6 months (*refer to HIM.PA.103 for generic bendamustine if pharmacy benefit*)

B. Non-Hodgkin B-Cell Lymphomas (must meet all)**:**
1. One of the following diagnoses (a through k):
   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. Follicular lymphoma;
   c. Gastric MALT lymphoma;
   d. Nongastric MALT lymphoma;
   e. Nodal marginal zone lymphoma;
   f. Splenic marginal zone lymphoma;
   g. Mantle cell lymphoma;
   h. Diffuse large B-cell lymphoma (DLBCL) (*as subsequent therapy*);*
   i. AIDS-related B-cell lymphoma (*as subsequent therapy*);*
   j. Monomorphic post-transplant lymphoproliferative disorder (PTLD) (B-cell type) (*as subsequent therapy*);*
   k. High-grade B-cell lymphomas: not otherwise specified or with translocations of MYC and BCL2 and/or BCL6 (double/triple hit lymphoma) (*as subsequent therapy*);*

   **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 nodal/splenic marginal zone lymphoma or gastric/nongastric MALT lymphoma, prescribed in combination with rituximab or Gazyva*;
5. For mantle cell lymphoma, prescribed in combination with rituximab;
6. 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*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Commercial/Medicaid – 6 months
HIM – 6 months (*refer to HIM.PA.103 for generic bendamustine if pharmacy benefit*)

C. NCCN Recommended Uses (off-label) (must meet all)**:**
1. Diagnosis of one of the following (a, b, c, d, e, f, or g):
   a. Classic or nodular lymphocyte-predominant Hodgkin lymphoma (HL) (*as subsequent therapy*);*
   b. Pediatric HL (*as re-induction or subsequent therapy*);*
   c. Multiple myeloma (MM);
   d. T-cell lymphomas (i, ii, iii, or iv):
      i. Hepatosplenic T-cell lymphoma (HSTCL) (*as subsequent therapy*);*
      ii. Adult T-cell leukemia/lymphoma (ATLL) (*as subsequent therapy*);*
      iii. Peripheral T-cell lymphoma (PTCL) (*as subsequent therapy*)*: relapsed/refractory ALCL, peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma,

nodal peripheral T-cell lymphoma with T-follicular helper (TFH) phenotype, or follicular T-cell lymphoma;
iv. Breast implant-associated ALCL (*as subsequent therapy*);*
e. Waldenstrom's macroglobulinemia (i.e., lymphoplasmacytic lymphoma);
f. Systemic light chain amyloidosis (SLCA) in combination with dexamethasone (*as subsequent therapy*);*
g. Hematopoietic cell transplantation in combination with etoposide, cytarabine, and melphalan for NHL without central nervous system (CNS) disease or for HL;

**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. 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*).*

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Commercial/Medicaid – 6 months
HIM – 6 months (*refer to HIM.PA.103 for generic bendamustine if pharmacy benefit*)

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 Belrapzo, Bendeka, Treanda, or Vivimusta 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 (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*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Commercial/Medicaid – 12 months
HIM – 12 months (*refer to HIM.PA.103 for generic bendamustine if pharmacy benefit*)

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

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
FDA: Food and Drug Administration
HL: Hodgkin lymphoma
HSTCL: hepatosplenic gamma-delta T-cell lymphoma
MF: mycosis fungoides
MM: multiple myeloma
NCCN: National Comprehensive Cancer Network
NHL: non-Hodgkin lymphoma
PTCL: peripheral T-cell lymphoma
PTLD: post-transplant lymphoproliferative disorder
SLCA: systemic light chain amyloidosis
SLL: small lymphocytic lymphoma
SS: Sezary syndrome

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.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Examples of primary therapies (NCCN)		
DLBCL		
RCHOP (Rituxan® [rituximab], cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies
EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + Rituxan® (rituximab)	Varies	Varies
AIDS-related B-cell lymphoma		
EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + Rituxan® (rituximab)	Varies	Varies
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + Rituxan® (rituximab)	Varies	Varies
PTCL		
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies
EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)	Varies	Varies
ATLL		
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies
HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine	Varies	Varies
HSTCL		
DHAP (dexamethasone, cisplatin, cytarabine)	Varies	Varies
ICE (ifosfamide, carboplatin, etoposide)	Varies	Varies
MM		
Bortezomib/liposomal doxorubicin/dexamethasone	Varies	Varies
Carfilzomib/lenalidomide/dexamethasone	Varies	Varies
Daratumumab/bortezomib /dexamethasone	Varies	Varies
Monomorphic PTLD (B-cell type)		
RCHOP (Rituxan® [rituximab], cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies
RCEPP (Rituxan® [rituximab], cyclophosphamide, etoposide, prednisone, procarbazine)	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
SLCA		
Daratumumab and hyaluronidase-fihj/bortezomib/cyclophosphamide/dexamethasone	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 Belrapzo, Treanda: 100 mg/m^2 IV over 30 minutes on days 1 and 2 of a 28-day cycle, up to 6 cycles 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 Belrapzo, Treanda: 120 mg/m^2 IV over 60 minutes on days 1 and 2 of a 21-day cycle, up to 8 cycles 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)	Solution (single-dose vial): 45 mg/0.5 mL; 180 mg/2 mL 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; June 2022. Available at: www.belrapzo.com. Accessed June 24, 2022.
2. Bendeka Prescribing Information. North Wales, PA: Teva Pharmaceuticals USA, Inc.; October 2021. Available at: http://www.bendeka.com/. Accessed June 24, 2022.
3. Treanda Prescribing Information. North Wales, PA: Teva Pharmaceuticals USA, Inc.; June 2021. Available at: http://treandahcp.com/. Accessed June 24, 2022.
4. Vivimusta Prescribing Information. Princeton, NJ: Slayback Pharma; December 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/212209s000lbl.pdf. Accessed December 27, 2022.
5. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed June 24, 2022.
6. National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 3.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed June 24, 2022.
7. National Comprehensive Cancer Network. B-cell Lymphomas Version 4.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed June 24, 2022.
8. National Comprehensive Cancer Network. Hodgkin Lymphoma Version 2.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf. Accessed June 24, 2022.
9. National Comprehensive Cancer Network. Multiple Myeloma Version 5.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed June 24, 2022.
10. National Comprehensive Cancer Network. T-cell Lymphomas Version 2.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf. Accessed June 24, 2022.
11. National Comprehensive Cancer Network. Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma Version 3.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf. Accessed June 24, 2022.

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
C9399	Unclassified drugs or biologicals (Vivimusta)
J9999	Not otherwise classified, antineoplastic drugs (Vivimusta)

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Age and dosing added Safety information removed. NCCN recommended uses added separately. Removed HCPCS code for bevacizumab. Removed ICD-10-CM codes.	09.05.17	11.17
4Q 2018 annual review: HIM-Medical Benefit added; summarized NCCN and FDA-approved uses for improved clarity; added age requirement and 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.	07.17.18	11.18
Added Commercial line of business to policy.	10.08.19	
4Q 2019 annual review: added HIM* line of business for Treanda based on formulary status; 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; references reviewed and updated.	08.14.19	11.19
4Q 2020 annual review: HIM-Medical Benefit line of business removed; off-label criteria sets combined into one - additional criteria limited to subsequent therapy requirement; appendix B prior therapy examples truncated; references reviewed and updated.	08.11.20	11.20
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 to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	06.28.21	11.21
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. Template changes applied to other diagnoses/indications.	06.24.22	11.22
RT4: added new dosage form Vivimusta; removed reference to HIM.PA.103 formulary exception policy for Belrapzo and Bendeka as these brands require PA on at least one HIM state formulary (FL).	12.28.22	

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.