

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

Reference Number: ERX.SPA.268

Effective Date: 12.01.18

Last Review Date: 11.22

Line of Business: Commercial, Medicaid

[Revision Log](#)

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

### Description

Bendamustine hydrochloride (Belrapzo<sup>®</sup>, Bendeka<sup>®</sup>, Treanda<sup>®</sup>) is an alkylating drug.

### FDA Approved Indication(s)

Belrapzo, Bendeka, and Treanda 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, lab results or other clinical information) supporting that member has met all approval criteria.*

*Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.*

It is the policy of health plans affiliated with Envolve Pharmacy Solutions<sup>™</sup> that Belrapzo, Bendeka, and Treanda 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  $\geq$  18 years;
4. Prescribed in combination with rituximab, Arzerra<sup>®</sup>, or Gazyva<sup>®</sup>;
5. Request meets one of the following (a or b):\*
  - a. Dose does not exceed 100 mg/m<sup>2</sup> 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: 6 months**

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

1. Diagnosis of one of the following (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  $\geq$  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<sup>2</sup> 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: 6 months**

**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;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age  $\geq$  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: 6 months**

**D. Other diagnoses/indications**

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**II. Continued Therapy**

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, or documentation supports that member is currently receiving Belrapzo, Bendeka, or Treanda 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<sup>2</sup> on Days 1 and 2 of a 28-day cycle, up to 6 cycles;
    - ii. Non-Hodgkin indolent B-cell lymphoma: 120 mg/m<sup>2</sup> on Days 1 and 2 of a 21-day cycle, up to 8 cycles;
  - b. New dose is supported by practice guideline 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: 12 months**

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.

**Approval duration: Duration of request or 6 months (whichever is less);** or

2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**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 policy – ERX.PA.01 or evidence of coverage documents.

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

ALCL: anaplastic large cell lymphoma	MF: mycosis fungoides
ATLL: adult T-cell leukemia/lymphoma	MM: multiple myeloma
CLL: chronic lymphocytic leukemia	NCCN: National Comprehensive Cancer Network
CNS: central nervous system	NHL: non-Hodgkin lymphoma
DLBCL: diffuse large B-cell lymphoma	PTCL: peripheral T-cell lymphoma
FDA: Food and Drug Administration	PTLD: post-transplant lymphoproliferative disorder
HL: Hodgkin lymphoma	SLCA: systemic light chain amyloidosis
HSTCL: hepatosplenic gamma-delta T-cell lymphoma	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 and may require prior authorization.*

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
<b>Examples of primary therapies (NCCN)</b>		
<b>DLBCL</b>		
RCHOP (Rituxan® [rituximab], cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies
EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + Rituxan® (rituximab)	Varies	Varies
<b>AIDS-related B-cell lymphoma</b>		
EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + Rituxan® (rituximab)	Varies	Varies
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + Rituxan® (rituximab)	Varies	Varies
<b>PTCL</b>		
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies
CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)	Varies	Varies
<b>ATLL</b>		
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies
HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine	Varies	Varies
<b>HSTCL</b>		
DHAP (dexamethasone, cisplatin, cytarabine)	Varies	Varies
ICE (ifosfamide, carboplatin, etoposide)	Varies	Varies
<b>MM</b>		
Bortezomib/liposomal doxorubicin/dexamethasone	Varies	Varies
Carfilzomib/lenalidomide/dexamethasone	Varies	Varies
Daratumumab/bortezomib /dexamethasone	Varies	Varies
<b>Monomorphic PTLD (B-cell type)</b>		
RCHOP (Rituxan® [rituximab], cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies
RCEPP (Rituxan® [rituximab], cyclophosphamide, etoposide, prednisone, procarbazine)	Varies	Varies
<b>SLCA</b>		
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 monoethioglycerol
  - Treanda: patients with a history of a hypersensitivity reaction to bendamustine
- Boxed warning(s): none reported

#### V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
CLL/SLL*	Bendeka: 100 mg/m <sup>2</sup> IV over 10 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles  Belrapzo, Treanda: 100 mg/m <sup>2</sup> IV over 30 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 <sup>2</sup> IV over 10 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles  Belrapzo, Treanda: 120 mg/m <sup>2</sup> IV over 60 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)	Solution (multiple-dose vial): 100 mg/4 mL

Drug Name	Availability
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](http://www.belrapzo.com). Accessed June 24, 2022.
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10. National Comprehensive Cancer Network. Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma Version 3.2022. Available at: [https://www.nccn.org/professionals/physician\\_gls/pdf/waldenstroms.pdf](https://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf). Accessed June 24, 2022.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	07.17.18	11.18
4Q 2019 annual review: added hepatosplenic gamma-delta T-cell lymphoma to non-Hodgkin T-cell lymphomas (off-label) uses and related therapeutic alternatives to Appendix B; added additional therapeutic alternatives to Appendix B with NCCN category 1: MM; references reviewed and updated.	08.14.19	11.19
4Q 2020 annual review: 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: 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.	06.28.21	11.21
4Q 2022 annual review: added Belrapzo; 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.	06.24.22	11.22

**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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.

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