Clinical Policy Title:	bendamustine
Policy Number:	RxA.352
Drug(s) Applied:	Bendeka®, Treanda®, Belrapzo®
Original Policy Date:	03/06/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

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

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
bendamustine hydrochloride (Bendeka®, Treanda®, Belrapzo®)	CLL/SLL	Bendeka®: 100 mg/m^2 intravenously over 10 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles Treanda®: 100 mg/m^2 intravenously over 30 minutes on days 1 and 2 of a 28-day cycle, up to 6 cycles Belrapzo®: 100 mg/m^2 intravenously over 30 minutes on days 1 and 2 of a 28-day cycle, up to 6 cycles	100 mg/m^2 on days 1 and 2 every 28 days
	Indolent B-cell lymphoma	Bendeka®: 120 mg/m^2 intravenously over 10 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles	120 mg/m^2 on days 1 and 2 every 21 days

		Treanda®: 120 mg/m^2 intravenously over 60 minutes on days 1 and 2 of a 21-day cycle, up to 8 cycles Belrapzo®:120 mg/m^2 intravenously over 60 minutes on days 1 and 2 of a 21-day cycle, up to 8 cycles	

Dosage Forms

- bendamustine (Bendeka®): 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
- bendamustine (Belrapzo®): Solution (multiple-dose vial): 100 mg/4 mL

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

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. Request meets one of the following (a or b):*
   a. Dose does not exceed (i or ii):
      i. Bendeka®: 100 mg/m^2 on Days 1 and 2 of a 28-day cycle, up to 6 cycles;
      ii. Treanda®: 100 mg/m2 on Days 1 and 2 of a 28-day cycle, up to 6 cycles;
      iii. Belrapzo®: 100 mg/m^2 intravenously over 30 minutes 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: 6 months
Medicaid: 6 months

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

1. One of the following diagnoses (a through j):
   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;
i. AIDS-related B-cell lymphoma;
j. Monomorphic post-transplant lymphoproliferative disorder (PTLD) (B-cell type);

2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. If the member has a diagnosis of diffuse large B-cell lymphoma, AIDS-related B-cell lymphoma, or monomorphic PTLD (B-cell type), member has used appropriate prior therapy (see Appendix B for examples);
5. Request meets one of the following (a or b):*
   a. Dose does not exceed (i or ii):
      i. Bendeka®: 120 mg/m^2 on Days 1 and 2 of a 21-day cycle, up to 8 cycles;
      ii. Treanda®: 120 mg/m^2 on Days 1 and 2 of a 21-day cycle, up to 8 cycles;
      iii. Belrapzo®: 120 mg/m^2 intravenously 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: 6 months
Medicaid: 6 months

C. Non-Hodgkin T-Cell Lymphomas (off-label) (must meet all)**:**

1. One of the following diagnoses (a, b, c, d, or e):
   a. Peripheral T-cell lymphoma (PTCL);
   b. Mycosis fungoides (MF)/Sezary syndrome (SS);
   c. Primary cutaneous CD30+ T-cell lymphoproliferative disorders;
   d. Adult T-cell leukemia/lymphoma;
   e. Hepatosplenic gamma-delta T-cell lymphoma;
   f. Breast implant -associated anaplastic large cell lymphoma (BIA-ALCL);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. If the member has a diagnosis of PTCL or adult T-cell leukemia/lymphoma, member has used appropriate prior therapy (see Appendix B for examples);
5. If member has a diagnosis of primary cutaneous CD30+ T-cell lymphoproliferative disorders, medication is prescribed as a single-agent therapy for relapsed/refractory disease;
6. If the member has the diagnosis of Breast implant -associated anaplastic large cell lymphoma medication is prescribed as second line and subsequent therapy for relapsed/refractory disease as single agent (see appendix B for examples);
7. If member has a diagnosis of hepatosplenic gamma-delta T-cell lymphoma, medication is prescribed as a single-agent therapy for refractory disease after 2 primary therapies (see Appendix B for examples);
8. 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: 6 months
Medicaid: 6 months

D. Hodgkin Lymphoma (off-label) (must meet all)**:**
1. Diagnosis of classical Hodgkin lymphoma (HL);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Disease is relapsed or refractory;
5. 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: 6 months
Medicaid: 6 months

E. Multiple Myeloma (off-label) (must meet all)**:**
1. Diagnosis of multiple myeloma (MM);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Member has used appropriate prior therapy (see Appendix B for examples);
5. 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: 6 months
Medicaid: 6 months

F. Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma (off-label) (must meet all)**:**
1. Diagnosis of Waldenstrom's macroglobulinemia (i.e., lymphoplasmacytic lymphoma);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
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: 6 months
Medicaid: 6 months

G. Pediatric Hodgkin Lymphoma (off-label) (must meet all):
1. Diagnosis of pediatric hodgkin lymphoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≤ 18 years; Per the Pediatric Hodgkin Lymphoma panel may also be applicable to adolescent and young adult patients up to age 39 years;

4. Request drug is given as re-induction therapy or subsequent therapy in combination with brentuximab vedotin, for relapsed or refractory disease as a consideration in patients heavily pre-treated (with platinum or anthracycline-based chemotherapy) or if a decrease in cardiac function observed;
5. If given with ISRT should meet one of the following:
   a. Stage other than IIIB or IVB;
   b. No prior exposure to RT;
   c. Duration of CR1 >1 year;
   d. Absence of extranodal disease or B symptoms at relapse;
6. 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: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

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

1. Member is currently receiving medication that has been authorized by RxAdvance, or documentation supports that member is currently receiving 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:
         a) Bendeka®: 100 mg/m^2 on Days 1 and 2 of a 28-day cycle, up to 6 cycles;
         b) Treanda®: 100 mg/m^2 Days 1 and 2 of a 28-day cycle, up to 6 cycles;
         c) Belrapzo®: 100 mg/m^2 intravenously over 30 minutes on days 1 and 2 of a 28-day cycle, up to 6 cycles
      ii. Non-Hodgkin indolent B-cell lymphoma:
         a) Bendeka®: 120 mg/m^2 on Days 1 and 2 of a 21-day cycle, up to 8 cycles;
         b) Treanda®: 120 mg/m2 on days 1 and 2 of a 21-day cycle, up to 8 cycles;
         c) Belrapzo®: 120 mg/m^2 intravenously 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: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
CLL: Chronic Lymphocytic Leukemia
FDA: Food and Drug Administration
HL: Hodgkin 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
SLL: Small Lymphocytic Lymphoma
SS: Sezary syndrome
ISRT: Involved-site radiation therapy
RT: Radio therapy
CR1: first complete remission
BIA-ALCL: Breast implant -associated anaplastic large cell lymphoma

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/Maximum Dose
Examples of first-line therapy for diffuse large B-cell lymphoma		
RCHOP (Rituxan® [rituximab], cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies
EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + Rituxan® (rituximab)	Varies	Varies
RCEPP (Rituxan® [rituximab], cyclophosphamide, etoposide, prednisone, procarbazine)	Varies	Varies
RCDOP (Rituxan® [rituximab], cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)	Varies	Varies
RGCVP (Rituxan® [rituximab], gemcitabine, cyclophosphamide, vincristine, prednisolone)	Varies	Varies
Examples of first-line therapy for AIDS-related B-cell lymphomas		
EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + Rituxan® (rituximab)	Varies	Varies
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + Rituxan® (rituximab)	Varies	Varies
Examples of first-line therapy for PTCL		
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
Examples of first-line therapy for adult T-cell leukemia/lymphoma		
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies
CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)	Varies	Varies
EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)	Varies	Varies
HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine	Varies	Varies
Examples of primary therapy for hepatosplenic gamma-delta T-cell lymphoma		
CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)	Varies	Varies
DHAP (dexamethasone, cisplatin, cytarabine)	Varies	Varies
EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)	Varies	Varies
ICE (ifosfamide, carboplatin, etoposide)	Varies	Varies
IVAC (ifosfamide, etoposide, cytarabine)	Varies	Varies
Examples of primary therapy for MM		
Bortezomib/liposomal doxorubicin/dexamethasone	Varies	Varies
Carfilzomib (twice weekly)/ dexamethasone	Varies	Varies
Carfilzomib/lenalidomide/dexamethasone	Varies	Varies
Daratumumab/bortezomib /dexamethasone	Varies	Varies
Examples of chemoimmunotherapy for monomorphic PTLD (B-cell type)		
RCHOP (Rituxan® [rituximab], cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies
RCEPP (Rituxan® [rituximab], cyclophosphamide, etoposide, prednisone, procarbazine)	Varies	Varies
RCVP (Rituxan® [rituximab], cyclophosphamide, vincristine, prednisone)	Varies	Varies
RCEOP (Rituxan® [rituximab], cyclophosphamide, etoposide, vincristine, prednisone)	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/Maximum Dose
Examples of primary therapy of Breast implant -associated anaplastic large cell lymphoma (T- cell)		
Brentuximab vedotin + CHP (Cyclophosphamide, doxorubicin, prednisone)	Varies	Varies
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies
CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)	Varies	Varies
Dose adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)	Varies	Varies

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Bendeka®, Belrapzo®: 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.

- Boxed warning(s):
  - None reported.

APPENDIX D: General Information

- Myelosuppression: Delay or reduce dose and restart treatment based on ANC and platelet count recovery.
- Infections: Monitor for fever and other signs of infection or reactivation of infections and treat promptly.
- Anaphylaxis and Infusion Reactions: Severe and anaphylactic reactions have occurred; monitor clinically and discontinue drug for severe reactions. Pre-medicate in subsequent cycles for milder reactions.
- Tumor Lysis Syndrome: May lead to acute renal failure and death; anticipate and use supportive measures in patients at high risk.
- Skin Reactions: Discontinue for severe skin reactions. Cases of SJS, DRESS and TEN, some fatal, have been reported.
- Hepatotoxicity: Monitor liver chemistry tests prior to and during treatment.
- Other Malignancies: Pre-malignant and malignant diseases have been reported.
- Extravasation Injury: Take precautions to avoid extravasation, including monitoring intravenous infusion site during and after administration.
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use an effective method of contraception.

References

1. Bendeka® Prescribing Information. North Wales, PA: Teva Pharmaceuticals USA, Inc.; November 2020. Available at: https://www.bendeka.com/. Accessed June 1, 2021.

2. Treanda® Prescribing Information. North Wales, PA: Teva Pharmaceuticals USA, Inc.; November 2019. Available at: https://www.treandahcp.com/. Accessed June 1, 2021.
3. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed June 1, 2021.
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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1. Policy title table was updated: Clinical Policy Title was updated to " bendamustine"; Drug(s) Applied was updated to "Bendeka®, Treanda®"; Line of Business Policy Applies to was updated to "All". 2. Clinical policy was updated: Approval duration was updated for both Initial and Continued Approval Criteria; Continued Approval was rephrased to "Currently receiving medication that has been authorized by RxAdvance.. ". 3. References were updated.	07/31/2020	09/14/2020
Policy was reviewed: 1. Clinical Policy drugs applied was updated to include "Belrapzo®" 2. Dosing Information dosing regimen was updated to include "Belrapzo®: 100 mg/m^2 intravenously over 30 minutes on days 1 and 2 of a 28-day cycle, up to 6 cycles…" 3. Dosage Forms was updated to include	06/01/2021	09/14/2021

"bendamustine (Belrapzo®): Solution (multiple-dose vial): 100 mg/4 mL…" 4. Statement about provider sample ''The provision of provider samples does not guarantee coverage…" was added to Clinical Policy. 5. Initial Approval Criteria I.A.4.a.iii was updated to include "Belrapzo®: 100 mg/m^2 intravenously over 30 minutes…" 6. Initial Approval Criteria I.B.5.a.iii was updated to include "Belrapzo®: 120 mg/m^2 intravenously on days…" 7. Initial Approval Criteria I.C.1.f was updated to include "Breast implant -associated anaplastic large cell lymphoma…" 8. Initial Approval Criteria I.C.6 was updated to include "If the member has the diagnosis of Breast implant…" 9. Initial Approval Criteria I.G was updated to include prescribing criteria for new indication "Pediatric Hodgkin Lymphoma (off-label)…" 10. Initial Approval Criteria and Continued Therapy Approval Criteria were updated to remove HIM approval duration. 11. Continued Therapy Approval Criteria II.A.3.a.i.c was updated to include "Belrapzo®: 100 mg/m^2 intravenously over 30 minutes…" 12. Continued Therapy Approval Criteria II.A.3.a.ii.c was updated to include "Belrapzo®: 120 mg/m^2 intravenously on days 1…" 13. Appendix A was updated to include abbreviations ISRT, RT, CR1, and BIA-ALCL. 14. Therapeutic Alternatives verbiage was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance..". 15. Appendix B: Therapeutic Alternatives was updated to include " 16. Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only".		

17. Appendix D was updated to include warnings and precautions “Myelosuppression: Delay or reduce dose and restart treatment based on ANC and platelet count recovery…” 18. References were reviewed and updated.		