Clinical Policy: Bendamustine (Bendeka, Treanda)

Reference Number: PA.CP.PHAR.307
Effective Date: 01/18
Last Review Date: 10/18

Coding Implications
Revision Log

Description
The intent of the criteria is to ensure that patients follow selection elements established by Pennsylvania Health and Wellness ® clinical policy for bendamustine hydrochloride (Bendeka®, Treanda®).

FDA Approved Indication(s)
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
It is the policy of Pennsylvania Health and Wellness ® that 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. 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/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 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. 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*);
3. Prescribed by or in consultation with an oncologist or hematologist;
4. 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;
   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. Non-Hodgkin T-Cell Lymphomas (off-label) (must meet all)**:**
a. One of the following diagnoses (a, b, c, or d):
   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;
b. 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*);
c. 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;
d. Prescribed by or in consultation with an oncologist or hematologist;
e. Age ≥ 18 years;
f. Request meets one of the following (a or b):
   a. Dose does not exceed the FDA approved maximum recommended dose for the relevant drug;
   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

D. Hodgkin Lymphoma (off-label) (must meet all)**:**
a. Diagnosis of classical Hodgkin lymphoma (HL);
b. Disease is relapsed or refractory;
c. Prescribed by or in consultation with an oncologist or hematologist;
d. Age ≥ 18 years;
e. Request meets one of the following (a or b):
   a. Dose does not exceed the FDA approved maximum recommended dose for the relevant drug;
   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

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. Request meets one of the following (a or b):
   a. Dose does not exceed the FDA-approved maximum recommended dose for the relevant drug;
   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

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. Request meets one of the following (a or b):
   a. Dose does not exceed the FDA-approved maximum recommended dose for the relevant drug;
   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

G. 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): CP.PMN.53

II. Continued Approval

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies; Member is responding positively to therapy;
2. 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;

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;

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 Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies; or
2. Refer to PA.CP.PMN.53

Background

Description/Mechanism of Action:

Bendamustine is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. Mechlorethamine and its derivatives form electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand DNA crosslinks. The bifunctional covalent linkage can lead to cell death via several pathways. Bendamustine is active against both quiescent and dividing cells. The exact mechanism of action of bendamustine remains unknown.

Formulations:

- Bendeka (bendamustine hydrochloride) Injection is supplied in individual cartons of 5 mL multiple-dose vials containing 100 mg of bendamustine hydrochloride as a ready-to-dilute solution:
  - 100 mg/4 mL (25 mg/mL)
- Treanda (bendamustine hydrochloride) Injection is supplied as a 90 mg/mL solution in individual cartons as follows:
  - 45 mg/0.5 mL of solution in a single-dose vial
  - 180 mg/2 mL of solution in a single-dose vial
- Treanda (bendamustine hydrochloride) for Injection is supplied in individual cartons as follows:
  - 25 mg white to off-white lyophilized powder in a 8 mL single-dose vial
  - 100 mg white to off-white lyophilized powder in a 20 mL single-dose vial

Appendices

Appendix A: Abbreviation Key

CLL: Chronic lymphocytic leukemia
DLBCL: Diffuse large B-cell lymphoma
MALT: Mucosa-associated lymphoid tissue
MF: Mycosis fungoides
MGUS: Monoclonal gammopathy of undetermined significance
NHL: Non-Hodgkin lymphoma
SCLC: Small cell lung cancer

SLL: Small lymphocytic lymphoma
SS: Sezary syndrome
ULN: Upper limit of normal
WHO: World Health Organization

Appendix B: 2016 WHO Classification of Mature B-Cell Neoplasms[7]

Mature B-Cell Neoplasms: Types and Subtypes*	
Chronic lymphocytic leukemia/small lymphocytic lymphoma	Large B-cell lymphoma with IRF4 rearrangement
Monoclonal B-cell lymphocytosis	Primary cutaneous follicle center lymphoma
B-cell prolymphocytic leukemia	Mantle cell lymphoma In situ mantle cell neoplasia
Splenic marginal zone lymphoma	
Hairy cell leukemia	Diffuse large B-cell lymphoma (DLBCL), NOS Germinal center B-cell type Activated B-cell type
Splenic B-cell lymphoma/leukemia, unclassifiable* Splenic diffuse red pulp small B-cell lymphoma Hairy cell leukemia-variant	T-cell/histiocyte-rich large B-cell lymphoma
Lymphoplasmacytic lymphoma Waldenstrom macroglobulinemia	Primary DLBCL of the central nervous system (CNS)
Monoclonal gammopathy of undetermined significance (MGUS), IgM μ heavy-chain disease ϒ heavy-chain disease α heavy-chain disease	Primary cutaneous DLBCL, leg type
	EBV+, DLBCL, NOS
	EBV+ mucocutaneous ulcer
	DLBCL associated with chronic inflammation
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A	Lymphomatoid granulomatosis
Plasma cell myeloma	Primary mediastinal (thymic) large B-cell lymphoma
Solitary plasmacytoma of bone	Intravascular large B-cell lymphoma
Extraosseous plasmacytoma	ALK+ large B-cell lymphoma
Monoclonal immunoglobulin deposition diseases	Plasmablastic lymphoma
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	Primary effusion lymphoma
Nodal marginal zone lymphoma	HHV8+ DLBCL, NOS
Pediatric nodal marginal zone lymphoma	Burkitt lymphoma
Follicular lymphoma In situ follicular neoplasia Duodenal-type follicular lymphoma	Burkitt-like lymphoma with 11q aberration
	High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements
	High-grade B-cell lymphoma, NOS
Pediatric-type follicular lymphoma	B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

*Based on clinical trials, examples of NHL B-cell lymphomas that may present with an indolent or low grade presentation include but are not limited to small lymphocytic lymphoma/B-cell

chronic lymphocytic leukemia, lymphoplasmacytic lymphoma (± Waldenstrom's macroglobulinemia), plasma cell myeloma/plasmacytoma, hairy cell leukemia, follicular lymphoma (grades I and II), marginal zone B-cell lymphoma, and mantle cell lymphoma.[1,2,5,6]

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
J9035	Injection, bevacizumab, 10 mg

ICD-10-CM Diagnosis Codes that Support Coverage Criteria

ICD-10-CM Codes	Description
B20	Human immune deficiency virus (HIV) disease
C81.00	Nodular lymphocyte predominant Hodgkin lymphoma, unspecified site
C81.10	Nodular sclerosis Hodgkin lymphoma, unspecified site
C81.20	Mixed cellularity Hodgkin lymphoma
C81.30	Lymphocyte depleted Hodgkin lymphoma
C81.40	Lymphocyte-rich Hodgkin lymphoma, unspecified site
C81.70	Other Hodgkin lymphoma, unspecified site
C82.00	Follicular lymphoma grade 1, unspecified site
C82.10	Follicular lymphoma grade 2, unspecified site
C82.20	Follicular lymphoma grade 3, unspecified site
C82.30	Follicular lymphoma grade IIIa, unspecified site
C82.40	Follicular lymphoma grade IIIb, unspecified site
C82.50	Follicle center lymphoma
C82.60	Cutaneous follicle center lymphoma, unspecified site
C82.80	Other types of follicular lymphoma, unspecified site
C83.00	Small cell B-cell lymphoma, unspecified site
C83.10	Mantle cell lymphoma, unspecified site
C83.30	Diffuse large B-cell lymphoma, unspecified site
C84.00	Mycosis fungoides, unspecified site
C84.10	Sezary disease, unspecified site
C84.40	Peripheral C-cell lymphoma, not classified, unspecified site
C84.60	Anaplastic large cell lymphoma, ALK positive, unspecified site
C84.70	Anaplastic large cell lymphoma, ALK negative, unspecified site
C85.00	Other specified types of non-Hodgkin lymphoma, unspecified site
C85.90	Non-Hodgkin lymphoma, unspecified, unspecified site

ICD-10-CM Codes	Description
C88.4	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma)
C86.2	Enteropathy type (intestinal) T-cell lymphoma
C86.5	Angioimmunoblastic T-cell lymphoma
C86.6	Primary cutaneous CD30-positive T-cell proliferations
C88.0	Waldenstrom's macroglobulinemia
C90.00	Multiple myeloma not having achieved remission
C90.02	Multiple myeloma in relapse
C91.10	Chronic lymphocytic leukemia of B-cell type, not having achieve remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
C91.50	Adult T-cell lymphoma leukemia (HTLV-1-associated) not having achieved remission
C91.52	Adult T-cell lymphoma leukemia (HTLV-1-associated) in relapse

References

1. Bendeka Prescribing Information. North Wales, PA: Teva Pharmaceuticals USA, Inc.; April 2018. Available at: http://www.bendeka.com/. Accessed July 17, 2018.
2. Treanda Prescribing Information. North Wales, PA: Teva Pharmaceuticals USA, Inc.; December 2017. Available at: http://treandahcp.com/. Accessed July 17, 2018.
3. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed July 11, 2018.
4. National Comprehensive Cancer Network. Chronic lymphocytic leukemia/small lymphocytic lymphoma Version 5.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed July 11, 2018.
5. National Comprehensive Cancer Network. B-cell lymphomas Version 4.2018. Available at nccn.org. Accessed July 17, 2018.
6. National Comprehensive Cancer Network. T-cell lymphomas Version 4.2018. Available at nccn.org. Accessed July 17, 2018.
7. National Comprehensive Cancer Network. Hodgkin lymphoma Version 3.2018. Available at nccn.org. Accessed July 18, 2018.
8. National Comprehensive Cancer Network. Multiple myeloma Version 4.2018. Available at nccn.org. Accessed July 17, 2018.
9. National Comprehensive Cancer Network. Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma Version 1.2018. Available at nccn.org. Accessed July 17, 2018.

Reviews, Revisions, and Approvals	Date	Approval 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.	07/18	