Clinical Policy: Bendamustine (Bendeka, Treanda)

Reference Number: CP.PHAR.307
Effective Date: 02/17
Last Review Date: 02/17

Coding Implications
Revision Log

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

Description

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

Policy/Criteria

It is the policy of health plans affiliated with Centene Corporation® 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) or small lymphocytic lymphoma (SLL);
2. Member does not have either of the following:
   a. Creatinine clearance (CrCl) < 40 mL/min;
   b. Moderate or severe hepatic impairment (i or ii):
      i. AST or ALT 2.5 to 10 times the upper limit of normal [ULN] and total bilirubin 1.5 to 3 times ULN;
      ii. Total bilirubin > 3 times ULN;
3. Member has no known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine, polyethylene glycol 400, propylene glycol, or monothioglycerol.

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**CLL and SLL, non-Hodgkin lymphoma (NHL) subtypes, are different manifestations of the same disease.*[4]

Approval duration: 3 months

B. Indolent B-Cell Non-Hodgkin Lymphoma*† (must meet all):

1. Diagnosis of indolent/low-grade B-cell non-Hodgkin lymphoma (NHL);
2. Disease progression during or within six months of treatment with rituximab or a rituximab-containing regimen;
3. Member does not have either of the following:
   a. CrCl < 40 mL/min;
   b. Moderate or severe hepatic impairment (i or ii):
      i. AST or ALT 2.5 to 10 times ULN and total bilirubin 1.5 to 3 times ULN;
      ii. Total bilirubin > 3 times ULN;
4. Member has no known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine, polyethylene glycol 400, propylene glycol, or monothioglycerol.

**See Appendix B for a complete list of B-cell lymphomas, including examples of types that may present in an indolent or low-grade fashion.*
†NHL subtypes (including B-cell lymphomas) for which NCCN recommends bendamustine therapy are listed under section I.C. "Other diagnoses/indications".

Approval duration: 3 months

C. Other diagnoses/indications: Refer to CP.PHAR.57 - Global Biopharm Policy.
1. The following NCCN recommended uses for Bendeka and Treanda, meeting NCCN categories 1, 2a, or 2b, are approved per the CP.PHAR.57 Global Biopharm Policy:
   a. Multiple myeloma;
   b. Small cell lung cancer (SCLC);
   c. Hodgkin lymphoma – classical;
   d. Non-Hodgkin lymphoma (NHL):
      i. B-cell lymphomas:
         a) Follicular lymphoma;
         b) Marginal zone lymphomas:
            1) Gastric MALT lymphoma;
            2) Non-gastric MALT lymphoma;
            3) Splenic marginal zone lymphoma;
         c) Mantle cell lymphoma;
         d) Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma;
         e) Diffuse large B-cell lymphoma;
         f) AIDS-related B-cell lymphoma;
         g) Primary cutaneous B-cell lymphomas;
      ii. T-cell lymphomas:
         a) Adult T-cell leukemia/lymphoma;
         b) Mycosis fungoides (MF)/Sezary syndrome (SS);
         c) Peripheral T-cell lymphoma;
         d) Primary cutaneous CD30+ T-cell lymphoproliferative disorders.

II. Continued Approval

A. All Indications (must meet all)**:**
1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. No disease progression or unacceptable toxicity;
3. Member has none of the following reasons to discontinue:
   a. Known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine, polyethylene glycol 400, propylene glycol, or monothioglycerol;
   b. Grade 4 (life-threatening) infusion reactions;
   c. CrCl < 40 mL/min;
   d. Moderate or severe hepatic impairment (i or ii):
      i. AST or ALT 2.5 to 10 times ULN and total bilirubin 1.5 to 3 times ULN;
      ii. Total bilirubin > 3 times ULN.

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy; or
2. Refer to CP.PHAR.57 - Global Biopharm Policy**.**

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

FDA Approved Indications:
Bendeka and Treanda (bendamustine hydrochloride) are alkylating drugs/intravenous formulations indicated for 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.

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
C88.4	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma)
C86.2	Enteropathy type (intestinal) T-cell lymphoma

ICD-10-CM Codes	Description
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

Reviews, Revisions, and Approvals	Date	Approval Date
Policy split from CP.PHAR.182 Excellus Oncology.	01/17	02/17

References

1. Bendeka prescribing information. North Wales, PA: Teva Pharmaceuticals USA, Inc.; June 2016. Available at http://bendeka.com/Pdf/PrescribingInformation.PDF. Accessed January 4, 2017.
2. Treanda prescribing information. North Wales, PA: Teva Pharmaceuticals USA, Inc.; October 2016. Available at http://www.treandahcp.com/pdf/TREANDA_final_PI.pdf. Accessed January 4, 2017.
3. Bendamustine hydrochloride. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed January 4, 2017.
4. Chronic lymphocytic leukemia/small lymphocytic lymphoma (Version 1.2017). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed January 4, 2017.
5. B-cell lymphomas (Version 1.2017). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed January 4, 2017.
6. Freedman AS, Friedberg JW. Classification of the hematopoietic neoplasms. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2016. Available at UpToDate.com. Accessed January 4, 2017.
7. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016; 127: 2375-2390.

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.

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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.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs and LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.