09-J2000-40

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Next Review: 07/08/20

Subject: Bendamustine HCl Injection

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Bendamustine is an alkylating agent; similar to other alkylating agents (e.g., cisplatin), it exerts its antineoplastic activity by cross-linking DNA and ultimately resulting in DNA single-strand and double-strand breaks. Bendamustine was originally developed in 1963 and has been used in Germany since 1971; however, Treanda was not approved by the US Food and Drug Administration (FDA) until March 2008. In December 2015, a new formulation of bendamustine, Bendeka, was approved by the FDA. Compared to Treanda, Bendeka has the advantages of allowing for a lower infusion volume (50 mL vs. 500 mL) and a faster infusion time (10 minutes vs. 30 to 60 minutes). Bendeka contains different solubilizes including monothioglycerol, and polyethylene glycol 400. In May 2018, Bendamustine Hydrochloride Injection (Eagle Pharmaceuticals, Inc) was approved by the FDA via the 505(b)(2) New Drug Application process providing an additional commercially available bendamustine formulation. In August 2018 the product was assigned the brand name of Belprazo. Belprazo is different from Treanda in that reconstitution of a lyophilized powder is not required during preparation [i.e., a “ready-to-dilute” (RTD) formulation]. It contains the same solubilizers as Bendeka; however, unlike Bendeka, Belrapzo is labeled to be diluted in a 500 mL infusion bag and administered over 30 to 60 minutes.

Currently, bendamustine is FDA-approved for the treatment of chronic lymphocytic leukemia (CLL) and indolent B-cell non-Hodgkin lymphoma (NHL). In addition to these FDA-approved indications, use in the treatment of a variety of other oncologic indications is supported by standard reference compendia (e.g., National Comprehensive Cancer Network [NCCN]). Bendamustine was granted orphan designation by the FDA, as sponsored by the innovator drug company, for the treatment of CLL in 2007 and for the treatment of indolent B-cell NHLs in 2013.

POSITION STATEMENT:

Initiation of bendamustine **meets the definition of medical necessity** when used for the treatment of an indication listed in Table 1 **AND** the indication-specific criteria and maximum allowable dosage criteria are met.

Table 1

Indications and Specific Criteria		
Indication	**Specific Criteria**	**Maximum Allowable Dosage**
Adult T-cell leukemia/lymphoma	**BOTH** of the following ("1" and "2"): 1. Bendamustine will be used as a single agent 2. Bendamustine is being used as second-line or later therapy for a member who did not respond to initial chemotherapy	• 120 mg/m^2 given twice (e.g., days 1 and 2) during every 21-day or 28-day cycle
AIDS-related B-cell lymphoma	**ALL** of the following ("1", "2", "3", and "4"): 1. Bendamustine is being used as second-line or later therapy 2. Bendamustine will be used as a single agent or in combination with rituximab* 3. Member has **ANY** of the following disease subtypes ("a", "b", or "c"): a. Diffuse large B-cell lymphoma b. Primary effusion lymphoma c. HHV8-positive diffuse large B-cell lymphoma, not otherwise specified (NOS) 4. The member is **NOT** a transplant candidate	• 120 mg/m^2 given twice (e.g., days 1 and 2) during every 21-day or 28-day cycle
Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)	**BOTH** of the following ("1" and "2"): 1. **EITHER** of the following ("a" or "b"): a. Bendamustine is being used as first-line therapy for previously untreated disease, **AND** bendamustine will be used as either a single agent or in combination with an anti-CD20 monoclonal antibody (i.e., obinutuzumab, ofatumumab, or rituximab) b. Bendamustine is being used as second-line or later therapy for relapsed or refractory disease, **AND** bendamustine	• 100 mg/m^2 given twice (e.g., days 1 and 2) during every 28-day cycle

	will be used in combination with rituximab (with or without the addition of ibrutinib) 2. The member does **NOT** have the del(17p) mutation	
Classical Hodgkin's lymphoma (CHL)	**BOTH** of the following ("1" and "2"): 1. Bendamustine will be used as **ANY** of the following regimens: a. Single agent therapy b. In combination with gemcitabine and vinorelbine c. In combination with brentuximab vedotin (Adcetris) 2. Bendamustine is being used as second-line or later therapy for relapsed or refractory disease	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 28-day cycle
Diffuse large B-Cell lymphoma (DLBCL) [including histologic transformation from follicular lymphoma or histologic transformation from marginal zone lymphoma]	**ALL** of the following ("1", "2", and "3"): 1. Bendamustine is being used as second-line or later therapy 2. One of the following treatment regimens will be used: a. Bendamustine as a single agent b. Bendamustine in combination with rituximab* c. Bendamustine in combination with rituximab* and polatuzumab vedotin-piiq (Polivy) **AND** the member has received at least **TWO** prior therapies for their condition 3. The member is **NOT** a transplant candidate	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 21-day or 28-day cycle
Follicular lymphoma	**EITHER** of the following ("1" or "2"): 1. **BOTH** of the following ("a" and "b"): a. Bendamustine is being used as first-line therapy b. Bendamustine will be used in combination with either rituximab or obinutuzumab (Gazyva) 2. **BOTH** of the following ("a" and "b"): a. Bendamustine is being used as second-line or later therapy for relapsed or refractory disease b. Bendamustine will be used as a single	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 21-day or 28-day cycle

	agent, or in combination with either rituximab or obinutuzumab	
Gastric MALT lymphoma	**EITHER** of the following ("1" or "2"): 1. **BOTH** of the following ("a" and "b"): a. Bendamustine is being used as first-line therapy b. Bendamustine will be used in combination with rituximab 2. **BOTH** of the following ("a" and "b"): a. Bendamustine is being used as second-line or later therapy for recurrent or progressive disease b. Bendamustine will be used as a single agent, or in combination with either rituximab or obinutuzumab	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 21-day or 28-day cycle
Hepatosplenic Gamma-Delta T-cell lymphoma	**BOTH** of the following ("1" and "2"): 1. Bendamustine will be used as a single agent 2. Member has refractory disease after two or more primary treatment regimens	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 21-day or 28-day cycle
High-grade B-cell lymphoma	**ALL** of the following ("1", "2", and "3"): 1. Bendamustine is being used as second-line or later therapy 2. Bendamustine will be used as a single agent or in combination with rituximab* 3. The member is **NOT** a transplant candidate	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 21-day or 28-day cycle
Lymphoplasmacytic lymphoma	**BOTH** of the following ("1" and "2"): 1. **EITHER** of the following ("a" or "b"): a. Member is symptomatic (e.g., hyperviscosity, neuropathy, symptomatic adenopathy or organomegaly, amyloidosis, cryoglobulinemia, cold agglutinin disease, presence of cytopenia), **AND** treatment is being used as primary therapy b. Treatment is for previously-treated relapsed or progressive disease 2. Bendamustine will be used as either single agent therapy **OR** in combination with rituximab	• 90 mg/m^2 given twice (e.g., days 1 and 2) during every 28-day cycle

Mantle cell lymphoma	**EITHER** of the following ("1" or "2"): 1. **BOTH** of the following ("a" and "b"): a. Bendamustine is being used as less aggressive induction therapy b. Bendamustine will be used in combination with rituximab* 2. **BOTH** of the following ("a" and "b"): a. Bendamustine is being used as second-line or later therapy for members with a partial response to induction therapy or for relapsed, refractory, or progressive disease b. Bendamustine will be used as a single agent or in combination with rituximab*	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 21-day or 28-day cycle
Multiple myeloma (MM)	**ALL** of the following ("1". "2", and "3"): 1. The member has previously-treated relapsed, refractory, or progressive disease 2. **ANY** of the following ("a", "b", "c", or "d"): a. Bendamustine will be used as a single agent b. Bendamustine will be used as doublet therapy in combination with dexamethasone c. Bendamustine will be used as triplet therapy in combination with both lenalidomide (Revlimid) and dexamethasone d. Bendamustine will be used as triplet therapy in combination with both bortezomib and dexamethasone 3. The member's baseline (i.e., within 90 days prior to initiating treatment with bendamustine) serum monoclonal protein (M-protein), as detected by serum protein electrophoresis (SPEP), is provided* **If the M-protein is undetectable by SPEP, baseline serum free light chain (SFLC) levels (kappa and lambda), as detected by serum free light chain assay (SFLCA), must also be provided*	Single-agent or doublet therapy: • 100 mg/m^2 given twice (e.g., days 1 and 2) during every 28-day cycle Triplet combination therapy: • 75 mg/m^2 given twice (e.g., days 1 and 2; days 1 and 8) during every 28-day cycle
Mycosis Fungoides (MF)/Sézary Syndrome	**BOTH** of the following ("1" and "2"): 1. Bendamustine will be used as single-agent systemic treatment (with or without skin-	• 120 mg/m^2 given twice (e.g., days 1 and 2) during every 21-day or

(SS)	directed therapy or radiation therapy) 2. **EITHER** of the following ("a" or "b"): a. Bendamustine will be used as second-line or later therapy for persistent, relapsed or refractory disease b. **BOTH** of the following ("i" and "ii"): i. Bendamustine is being used as initial primary therapy ii. Member has **EITHER** stage IV non-Sézary or visceral disease (solid organ), **OR** large cell transformation (LCT) with generalized cutaneous or extracutaneous lesions	28 day cycle
Nodal marginal zone lymphoma	**EITHER** of the following ("1" or "2"): 1. **BOTH** of the following ("a" and "b"): a. Bendamustine is being used as first-line therapy b. Bendamustine will be used in combination with rituximab 2. **BOTH** of the following ("a" and "b"): a. Bendamustine is being used as second-line or later therapy for refractory or progressive disease b. Bendamustine will be used in combination with either rituximab or obinutuzumab	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 21-day or 28-day cycle
Non-gastric MALT lymphoma	**EITHER** of the following ("1" or "2"): 1. **ALL** of the following ("a", "b", and "c"): a. Bendamustine is being used as first-line therapy b. Member has stage IV disease c. Bendamustine will be used in combination with rituximab 2. **BOTH** of the following ("a" and "b"): a. Bendamustine is being used as second-line or later therapy for recurrent, refractory or progressive disease b. Bendamustine will be used as a single agent, or in combination with either rituximab or obinutuzumab	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 21-day or 28-day cycle
Peripheral T-cell	**ALL** of the following ("1", "2", and "3"):	• 120 mg/m^2 given twice (e.g., days 1 and 2)

lymphoma (PTCL)	1. Bendamustine will be used as a single agent 2. Bendamustine will be used as second-line or later therapy for relapsed or refractory disease 3. The member has **ANY** of the following disease subtypes: a. Anaplastic large cell lymphoma (ALCL) b. Angioimmunoblastic T-cell lymphoma (AITL) c. Enteropathy-associated T-cell lymphoma (EATL) d. Follicular T-cell lymphoma e. Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) f. Nodal peripheral T-cell lymphoma with TFH phenotype g. Peripheral T-cell lymphoma, not otherwise specified (NOS)	during every 21-day or 28-day cycle
Post-Transplant Lymphoproliferative Disorder (PTLD)	**ALL** of the following ("1", "2", and "3"): 1. Treatment is used as second-line or later therapy for relapsed or refractory disease 2. Member was previously treated for B-cell type, monomorphic PTLD 3. Bendamustine will be used as either monotherapy or in combination with rituximab*	• 120 mg/m^2 given twice (e.g., days 1 and 2) during every 21-day or 28-day cycle
Primary cutaneous diffuse large B-cell lymphoma, leg type	**ALL** of the following ("1", "2", and "3"): 1. Bendamustine will be used as second-line or later therapy for relapsed or refractory disease 2. Bendamustine will be used as a single agent or in combination with rituximab 3. The member is **NOT** a transplant candidate	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 21-day or 28-day cycle
Primary cutaneous CD30+ T-cell lymphoproliferative disorders	**ALL** of the following ("1", "2", and "3"): 1. Member has progressive, refractory, or relapsed disease 2. Bendamustine will be used as a single agent 3. The member has **EITHER** of the following disease subtypes ("a" or "b"): a. Primary cutaneous anaplastic large cell lymphoma (ALCL) with multifocal lesions	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 21-day or 28-day cycle

	b. Cutaneous ALCL with regional nodes (excludes systemic ALCL)	
Splenic marginal zone lymphoma	**EITHER** of the following ("1" or "2"): 1. **ALL** of the following ("a", "b", or "c"): a. Member has had disease progression following splenectomy, or is not a surgical candidate (reason for non-candidacy must be provided) b. Bendamustine is being used as first-line medical therapy c. Bendamustine will be used combination with rituximab 2. **BOTH** of the following ("a" and "b"): a. Bendamustine is being used as second-line or later medical therapy for progressive or refractory disease b. Bendamustine will be used as a single agent, or in combination with either rituximab or obinutuzumab	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 21-day or 28-day cycle
Waldenström's macroglobulinemia	**ALL** of the following ("1", "2", and "3"): 1. **EITHER** of the following ("a" or "b"): a. Member is symptomatic (e.g., hyperviscosity, neuropathy, symptomatic adenopathy or organomegaly, amyloidosis, cryoglobulinemia, cold agglutinin disease, presence of cytopenia), **AND** treatment is being used as primary therapy b. Treatment is for previously-treated relapsed or progressive disease 2. Bendamustine will be used as either single agent therapy **OR** in combination with rituximab 3. The member's baseline (i.e., within 90 days prior to initiating treatment with bendamustine) serum IgM level is provided	• 90 mg/m^2 given twice (e.g., days 1 and 2) during every 28-day cycle
Other FDA-approved or NCCN supported diagnosis (not previously listed above)	**EITHER** of the following ("1" or "2"): 1. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or	• Dosage does not exceed the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guidelines for the

	package insert) 2. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation	diagnosis
**Obinutuzumab (Gazyva) may be substitute for rituximab in patients experiencing rare complications such as mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis – the specific complication must be provided*		
Approval duration: 6 months		

Continuation of bendamustine **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1", "2", and "3"):

1. An authorization or reauthorization for bendamustine has been previously approved by Florida Blue or another health plan in the past 2 years for an indication listed in Table 1, **OR** the member previously met **ALL** indication-specific initiation criteria
2. Member's disease has not progressed during treatment with bendamustine, **UNLESS** treatment is being used as palliative therapy
3. The dose of bendamustine does not exceed the maximum allowable dosage listed in Table 1 for the member's indication, **UNLESS** a higher dosage was previously authorized by Florida Blue

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved: bendamustine is indicated for the treatment of (1) chronic lymphocytic leukemia (CLL), and (2) indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. The recommended dosing for bendamustine is based on indication and is described in Table 2.

Table 2: Approved Dosing and Administration

Indication	Dosing/Administration	Dose Modifications
CLL	100 mg/m^2 IV over 30 minutes (for Belrapzo and Treanda) or 10 minutes (for Bendeka) on days 1	1. Hematologic toxicity a. Grade 3 or greater: reduce to 50 mg/m^2

	and 2 of a 28 day cycle, up to 6 cycles	on days 1 and 2 of each cycle b. Recurrence of grade 3 or greater: reduce to 25 mg/m^2 on days 1 and 2 of each cycle 2. Non-hematologic toxicity: clinically significant Grade 3 or greater, reduce to 50 mg/m^2 on days 1 and 2 of each cycle 3. Dose re-escalation may be considered
NHL	120 mg/m^2 IV over 60 minutes (for Belrapzo and Treanda) or 10 minutes (for Bendeka) on days 1 and 2 of a 21 day cycle, up to 8 cycles	1. Hematologic toxicity a. Grade 4: reduce the dose to 90 mg/m2 on days 1 and 2 of each cycle b. Recurrence of grade 4: reduce dose to 60 mg/m^2 on days 1 and 2 of each cycle 2. Non-hematologic toxicity a. Grade 3 or greater: reduce the dose to 90 mg/m^2 on days 1 and 2 of each cycle b. Recurrence of grade 3 or greater: reduce dose to 60 mg/m^2 on days 1 and 2 of each cycle
CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma; IV, intravenous		

- General dosing considerations: delay treatment for Grade 4 hematologic toxicity or clinical significant grade 2 or greater non-hematologic toxicity.
- Renal impairment: Do not use if CRC is < 40 mL/min. Use with caution in lesser degrees of renal impairment.
- Hepatic impairment: Do not use in moderate or severe hepatic impairment (Child-Pugh Category B or C). Use with caution in mild hepatic impairment.
- Do **NOT** use bendamustine injection with devices that contain polycarbonate or acrylonitrile-butadiene-styrene (ABS), including most Closed System Transfer Devices (CSTDs).

Product Availability:

- Belrapzo - 100 mg/4 mL solution in multiple-dose vials (25 mg/mL). Store refrigerated between 2°-8°C (36°- 46°F) and protect from light.
- Bendeka - 100 mg/4 mL solution in multiple-dose vials (25 mg/mL). Store refrigerated between 2°-8°C (36°- 46°F) and protect from light
- Treanda - 25 or 100 mg lyophilized powder in single-use vials that must be reconstituted prior to infusion. The solutions must be stored refrigerated between 2°- 8°C (36°- 46°F) and protected from light. The powder may be stored up to 25°C (77°F) with excursions permitted up to 30°C (86°F) and protected from light.

PRECAUTIONS:

Boxed Warning:

- None

Contraindications:

- Prior history of hypersensitivity reactions to bendamustine (Treanda, Bendamustine Hydrochloride Injection, and Bendeka), or polyethylene glycol 400, propylene glycol, or monothioglycerol (Bendamustine Hydrochloride Injection and Bendeka only)

Precautions/Warnings:

- **Myelosuppression**: Delay or reduce dose. Restart treatment based on ANC and platelet count recovery. Complications of myelosuppression may lead to death.
- **Infections**: Monitor for fever and other signs of infection and treat promptly.
- **Anaphylaxis and Infusion Reactions**: Severe and anaphylactic reactions have occurred; monitor clinically and discontinue bendamustine. Pre-medicate in subsequent cycles for milder reactions.
- **Tumor Lysis Syndrome**: Acute renal failure and death; anticipate and use supportive measures.
- **Skin Reactions**: Discontinue for severe skin reactions. Cases of SJS and TEN, some fatal, have been reported when bendamustine was administered concomitantly with allopurinol and other medications known to cause these syndromes.
- **Hepatotoxicity**: Fatal and serious cases of liver injury have been reported. Monitor liver chemistry tests prior to and during treatment
- **Other Malignancies**: Pre-malignant and malignant diseases have been reported.
- **Extravasation**: Assure good venous access and monitor infusion site during and after administration.
- **Embryo-fetal toxicity**: Fetal harm can occur when administered to a pregnant woman. Women should be advised to avoid becoming pregnant when receiving bendamustine.
- **Drug Interactions**: Concomitant CYP1A2 inducers or inhibitors have the potential to affect the exposure of bendamustine.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding (Treanda)

J9033	Injection, bendamustine HCl (Treanda), 1 mg

HCPCS Coding (Bendeka)

J9034	Injection, bendamustine HCl (Bendeka), 1 mg

HCPCS Coding (Belrapzo)

C9042	Injection, bendamustine HCl (Belrapzo), 1 mg (for hospital outpatient use ONLY)
J9999	Not otherwise classified, antineoplastic drugs

ICD-10 Diagnosis Codes That Support Medical Necessity:

B20 w/ C83.39	Human immunodeficiency virus [HIV] disease; Diffuse large B-cell lymphoma, extranodal and solid organ sites
C81.00 – C81.09	Nodular lymphocyte predominant Hodgkin lymphoma
C81.10 – C81.19	Nodular sclerosis classical Hodgkin lymphoma
C81.20 – C81.29	Mixed cellularity classical Hodgkin lymphoma
C81.30 – C81.39	Lymphocyte depleted classical Hodgkin lymphoma
C81.40 – C81.49	Lymphocyte-rich classical Hodgkin lymphoma
C81.70 – C81.79	Other classical Hodgkin lymphoma
C81.90 – C81.99	Hodgkin lymphoma, unspecified
C82.00 – C82.09	Follicular lymphoma grade I
C82.10 – C82.19	Follicular lymphoma grade II
C82.20 – C82.29	Follicular lymphoma grade III, unspecified
C82.30 – C82.39	Follicular lymphoma grade IIIa
C82.40 – C82.49	Follicular lymphoma grade IIIb
C82.60 – C82.69	Cutaneous follicle center lymphoma
C82.80 – C82.89	Other types of follicular lymphoma
C82.90 – C82.99	Follicular lymphoma, unspecified
C83.00 – C83.09	Small cell B-cell lymphoma
C83.10 – C83.19	Mantle Cell lymphoma
C83.30 – C83.39	Diffuse large B-cell lymphoma
C83.50 – C83.59	Lymphoblastic (diffuse) lymphoma
C83.80 – C83.89	Other non-follicular lymphoma
C83.90 – C83.99	Non-follicular (diffuse) lymphoma, unspecified
C84.40 – C84.49	Peripheral T-cell lymphoma, not classified
C84.60 – C84.69	Anaplastic large cell lymphoma, ALK-positive
C84.70 – C84.79	Anaplastic large cell lymphoma, ALK-negative
C85.20-C85.29	Mediastinal (thymic) large B-cell lymphoma
C85.80 – C85.89	Other specified types of non-Hodgkin lymphoma
C86.6	Primary cutaneous CD30-positive T-cell proliferations
C88.0	Waldenström macroglobulinemia
C88.4	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma]
C88.8	Other malignant immunoproliferative diseases
C90.00	Multiple myeloma not having achieved remission
C90.02	Multiple myeloma in relapse
C90.10	Plasma cell leukemia not having achieved remission
C90.12	Plasma cell leukemia in relapse
C90.20	Extramedullary plasmacytoma not having achieved remission
C90.22	Extramedullary plasmacytoma in relapse
C90.30	Solitary plasmacytoma not having achieved remission
C90.32	Solitary plasmacytoma in relapse
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved 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
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)
D47.Z9	Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) was found at the time of the last guideline review date. The following Local Coverage Determination (LCD) was reviewed on the last guideline review date: bendamustine hydrochloride (Treanda, Bendeka), (L33268) located at fcso.com.

DEFINITIONS:

None

RELATED GUIDELINES:

Bortezomib (Velcade) Injection, 09-J0000-92

Doxorubicin HCl Liposome (Doxil) Injection, 09-J0000-91

Ibrutinib (Imbruvica), 09-J2000-09

Idelalisib (Zydelig) Oral Tablet - 09-J2000-23

Lenalidomide (Revlimid), 09-J0000-08

Obinutuzumab (Gazyva), 09-J2000-07

Procarbazine (Matulane) Capsules, 09-J1000-59

Rituximab (Rituxan), 09-J0000-59

Thalidomide (Thalomid) Capsules, 09-J1000-56

Vorinostat (Zolinza) Capsules, 09-J1000-54

OTHER:

None.

REFERENCES:

1. Belrapzo (bendamustine hydrochloride injection) [package insert]. Eagle Pharmaceuticals, Inc. Woodcliff Lake (NJ): December 2018.
2. Bendeka (bendamustine) [package insert]. Teva Pharmaceuticals USA, Inc. North Wales (PA): April 2018.
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at: www.clinicalpharmacilogy-ip.com. Accessed 6/19/19.
4. Damaj G, Gressin R, Bouabdallah K, et al. Results from a prospective, open-label, phase II trial of bendamustine in refractory or relapsed T-cell lymphomas: the BENTLY trial. J Clin Oncol. 2013 Jan 1;31(1):104-10.
5. Eichhorst B, Fink AM, Bahlo J, et al; German CLL Study Group (GCLLSG). First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2016 Jul;17(7):928-42.
6. Fischer K, Cramer P, Busch R, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2011 Sep 10;29(26):3559-66.
7. Fischer K, Cramer P, Busch R, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2012 Sep 10;30(26):3209-16.
8. Gertz MA. Waldenström macroglobulinemia: 2017 update on diagnosis, risk stratification, and management. Am J Hematol. 2017 Feb;92(2):209-217.
9. Imbruvica (ibrutinib) [package insert]. Pharmacyclics LLC. Sunnyvale (CA): January 2019.
10. Knauf WU, Lissitchkov T, Aldaoud A, et al. Bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukaemia: updated results of a randomized phase III trial. Br J Haematol. 2012 Oct;159(1):67-77
11. Knop S, Straka C, Haen M, et al. The efficacy and toxicity of bendamustine in recurrent multiple myeloma after high-dose chemotherapy. Haematologica. 2005 Sep;90(9):1287-8.
12. Lentzsch S, O'Sullivan A, Kennedy RC, et al. Combination of bendamustine, lenalidomide, and dexamethasone (BLD) in patients with relapsed or refractory multiple myeloma is feasible and highly effective: results of phase 1/2 open-label, dose escalation study. Blood. 2012 May 17;119(20):4608-13.
13. Ludwig H, Kasparu H, Leitgeb C, et al. Bendamustine-bortezomib-dexamethasone is an active and well-tolerated regimen in patients with relapsed or refractory multiple myeloma. Blood. 2014 Feb 13;123(7):985-91.
14. Mey UJ, Brugger W, Schwarb H, et al. Bendamustine, lenalidomide and dexamethasone (BRd) has high activity as 2nd -line therapy for relapsed and refractory multiple myeloma - a phase II trial. Br J Haematol. 2017 Mar;176(5):770-782. Epub 2016 Dec 16.
15. Michael M, Bruns I, Bölke E, et al. Bendamustine in patients with relapsed or refractory multiple myeloma. Eur J Med Res. 2010 Jan 29;15(1):13-9.
16. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 6/18/18.
17. Moskowitz AJ, Hamlin PA Jr, Perales MA, et al. Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma. J Clin Oncol. 2013 Feb 1;31(4):456-60.
18. National Comprehensive Cancer Network. Cancer Guidelines. Cancer Guidelines and Drugs and Biologics Compendium. Accessed 6/13/19.

19. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines). B-cell Lymphomas (Version 4.2019) [cited 2019 Jun 19]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf
20. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines). Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Version 5.2019) [cited 2019 Jun 19]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf
21. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines). Hodgkin Lymphoma (Version 1.2019) [cited 2019Jun 19]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf
22. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines). Multiple Myeloma (Version 2.2019) [cited 2019 Jun 19]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf
23. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines). Primary Cutaneous Lymphomas (Version 2.2019) [cited 2019Jun 19]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pd
24. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines). Small Cell Lung Cancer (Version 1.2019) [cited 2019 Jun 19]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf
25. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines). T-Cell Lymphomas (Version 2.2019) [cited 2019 Jun 19]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf
26. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines). Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma (Version 2.2018) [cited 2019 Jun 19]. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
27. Offidani M, Corvatta L, Maracci L, et al. Efficacy and tolerability of bendamustine, bortezomib and dexamethasone in patients with relapsed-refractory multiple myeloma: a phase II study. Blood Cancer J. 2013 Nov 22;3:e162.
28. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2018 [cited 2019 Jun 13]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
29. Polivy (polatuzumab vedotin-piiq) [package insert]. Genentech, Inc. South San Francisco, CA: June 2019.
30. Rummel MJ, Niederle N, Maschmeyer G, et al.; Study group indolent Lymphomas (StiL). Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013 Apr 6;381(9873):1203-10
31. Santoro A, Mazza R, Pulsoni A, et al. Bendamustine in Combination With Gemcitabine and Vinorelbine Is an Effective Regimen As Induction Chemotherapy Before Autologous Stem-Cell Transplantation for Relapsed or Refractory Hodgkin Lymphoma: Final Results of a Multicenter Phase II Study. J Clin Oncol. 2016 Sep 20;34(27):3293-9.
32. Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol. 2016 Aug;17(8):1081-93.
33. Tedeschi A, Picardi P, Ferrero S, et al. Bendamustine and rituximab combination is safe and effective as salvage regimen in Waldenström macroglobulinemia. Leuk Lymphoma. 2015;56(9):2637-42.
34. Treanda (bendamustine) [package insert]. Teva Pharmaceuticals USA, Inc. North Wales (PA): April 2019.

35. Treon SP, Hanzis C, Tripsas C, et al. Bendamustine therapy in patients with relapsed or refractory Waldenström's macroglobulinemia. Clin Lymphoma Myeloma Leuk. 2011 Feb;11(1):133-5.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the BCBSF Pharmacy Policy Committee on 7/10/19.

GUIDELINE UPDATE INFORMATION:

06/15/14	New Medical Coverage Guideline.
06/15/15	Review and revision to guideline; consisting of updating position statement, dosing/administration, coding, and references.
10/01/15	Revision consisting of update to Program Exceptions section.
03/15/16	Revision consisting of update to description, dosage/administration, coding/billing, and references.
06/15/16	Review and revision to guideline consisting of updating the position statement and references.
01/01/17	Revision: added HCPCS code J9034.
02/15/17	Revision to guideline consisting of updating the description, position statement, and references based on an update to the NCCN guidelines for B-cell lymphomas.
07/15/17	Review and revision to guideline consisting of updating and reformatting the position statement and updating the precautions and references.
8/15/18	Review and revision to guideline consisting of updating the position statement, billing/coding, and references.
09/15/18	Revision to guideline consisting of updating the description section, dosage/administration section, precautions section, billing/coding, and references based on the FDA approval of the new product Bendamustine Hydrochloride Injection (Eagle Pharmaceuticals, Inc.)
04/01/19	Revision: added HCPCS code C9042 and added new Belrapzo name.
06/15/19	Revision to guideline consisting of updating the position statement and references based on updated NCCN guidelines.
08/15/19	Review and revision to guideline consisting of updating the position statement and references.