09-J2000-40

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Subject: Bendamustine HCl Injection

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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 does not require reconstitution of a lyophilized powder during preparation [i.e., a “ready-to-dilute” (RTD) formulation], and it 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) as per it’s package labeling. Bendeka contains different solubilizers 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 (NDA) process providing an additional commercially available bendamustine formulation. In August 2018 the product was assigned the brand name of Belrapzo. Belrapzo is different from Treanda and similar to Bendeka in that reconstitution of a lyophilized powder is not required during preparation. 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. In December 2022, another bendamustine product, Vivimusta from Slayback Pharmaceuticals, was approved by the FDA via the 505(b)(2) NDA process using Bendeka as the reference drug. Vivimusta is a RTD formulation like Bendeka and Belrapzo but contains dehydrated alcohol vs. propylene glycol. Viuvmusta must be diluted in a 250 mL infusion bag and is infused over 20 minutes as per it’s package labeling. Starting in 2023, multiple manufacturers began producing AP-rated generics (approved via the ANDA pathway) of Treanda making many different lyophilized powder bendamustine products available for use.

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.

- For brand Vivimusta (HCPCS - J9056) **ONLY - EITHER** of the following must apply ("a" or "b"):
    a. Member has a contraindication to **ALL** other available bendamustine products [Treanda and its generic equivalents (J9033), Bendeka (J9034), and Belrapzo (J9036)], **AND** the contraindication is not applicable to Vivimusta - the specific contraindication(s) and rationale for using Vivimusta must be provided
    b. Member has tried and had intolerable adverse effects to at least **TWO** other available bendamustine products [Treanda and its generic equivalents (J9033), Bendeka (J9034), and Belrapzo (J9036)], **AND** the intolerance is not expected to occur with Vivimusta - the specific intolerance(s) and rationale for using Vivimusta must be provided. Also, **BOTH** of the following are required:
        i. A completed MedWatch form (FDA 3500) must be submitted: https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda
        ii. A completed Naranjo Adverse Drug reaction probability scale must be submitted: https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf

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
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	• 100 mg/m^2 given twice (e.g., days 1 and 2) during every 28-day cycle

	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 will be used in combination with rituximab (with or without the addition of ibrutinib) 2. The member does **NOT** have the del(17p) mutation	
Classic Hodgkin 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 carboplatin and etoposide c. In combination with gemcitabine and vinorelbine d. 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 21-day or 28-day cycle
Cold agglutinin disease (CAD)	**BOTH** of the following ("1" and "2"): 1. Member has symptomatic, primary cold agglutinin disease 2. Bendamustine will be used in combination with rituximab	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 21-day or 28-day cycle
Diffuse large B-Cell lymphoma (DLBCL) [including histologic transformation from indolent lymphomas such as follicular lymphoma or nodal	**ALL** of the following ("1", "2", and "3"): 1. Bendamustine is being used as second-line or later therapy, or as bridging therapy for members with intention to proceed to CAR T-cell therapy 2. One of the following treatment regimens will be used: a. Bendamustine as a single agent	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 21-day or 28-day cycle

marginal zone lymphoma]	b. Bendamustine in combination with rituximab* c. Bendamustine in combination with polatuzumab vedotin (with or without rituximab) 3. The member is **NOT** intending to proceed to a transplant	
Extranodal marginal zone lymphoma (EMZL) of non-gastric sites (noncutaneous) [a.k.a., non-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. **ALL** of the following ("a", "b", and "c"): 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 c. Member has not been previously treated with bendamustine for their disease	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 21-day or 28-day cycle
Extranodal marginal zone lymphoma of the stomach [a.k.a., gastric mucosa-associated lymphoid tissue (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. **ALL** of the following ("a", "b", and "c"): 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

	c. Member has not been previously treated with bendamustine for their disease	
Follicular lymphoma [a.k.a., classic 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. One of the following treatment regimens will be used: i. Bendamustine as a single agent ii. Bendamustine in combination with rituximab or obinutuzumab (Gazyva)	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 21-day or 28-day cycle
Hematopoietic cell transplantation conditioning regimen	**BOTH** of the following ("1" and "2"): 1. Bendamustine is being use as part of a conditioning regimen for autologous hematopoietic cell transplantation 2. Bendamustine will be used in combination with etoposide, cytarabine and melphalan (BeEAM)	• 200 mg/m^2 x 2 doses given prior to autologous hematopoietic cell transplantation
Hepatosplenic 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 prior 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 [including high-grade B-cell lymphomas, NOS; and high-grade B-cell lymphomas with translocations of MYC and BCL2 and/or BCL6	**ALL** of the following ("1", "2", and "3"): 1. Bendamustine is being used as second-line or later therapy, or as bridging therapy for members with intention to proceed to CAR T-cell therapy 2. **ONE** of the following treatment regimens will be used:	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 21-day or 28-day cycle

(double/triple hit lymphoma)]	a. Bendamustine as a single agent b. Bendamustine in combination with rituximab* c. Bendamustine in combination with polatuzumab vedotin (with or without rituximab) 3. The member is **NOT** intending to proceed to a transplant	
HIV-related B-cell lymphoma	**ALL** of the following ("1", "2", "3", and "4"): 1. Bendamustine is being used as second-line or later therapy, or as bridging therapy for members with intention to proceed to CAR T-cell therapy 2. **ONE** of the following treatment regimens will be used (see exception for plasmablastic lymphoma): a. Bendamustine as a single agent b. Bendamustine in combination with rituximab* c. Bendamustine in combination with polatuzumab vedotin (with or without rituximab) 3. Member has **ANY** of the following disease subtypes ("a", "b", "c" or "d"): a. HIV-related diffuse large B-cell lymphoma b. Primary effusion lymphoma c. HHV8-positive diffuse large B-cell lymphoma, not otherwise specified (NOS) d. Plasmablastic lymphoma [**NOT** to be used in combination with rituximab (i.e., only bendamustine monotherapy or bendamustine + polatuzumab vedotin)] 4. The member is **NOT** intending to proceed to a transplant	• 120 mg/m^2 given twice (e.g., days 1 and 2) during every 21-day or 28-day cycle
Lymphoplasmacytic lymphoma	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)

(Including Bing Neel syndrome)		during every 28-day cycle
Mantle cell lymphoma	**ANY** of the following ("1", "2", or "3"): 1. **BOTH** of the following ("a" and "b"): a. Bendamustine is being used as aggressive induction therapy b. **EITHER** of the following treatment regimens will be used: i. Bendamustine is being used in combination with rituximab, followed by rituximab in combination with high dose cytarabine ii. Bendamustine will be used as a component of RBAC500 (rituximab, bendamustine, and cytarabine) regimen* 2. **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* 3. **BOTH** of the following ("a" and "b"): a. Bendamustine is being used as second-line or later therapy for members with have stable disease or a partial response to induction therapy; or for relapsed, refractory, or progressive disease b. **EITHER** of the following treatment regimens will be used: i. Bendamustine will be used in combination with rituximab* ii. Bendamustine will be used as a component of RBAC500 (rituximab, bendamustine, and cytarabine) regimen*	• 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"):	Single-agent or doublet therapy:

	1. The member has previously treated relapsed, refractory, or progressive disease 2. The member has received at least **THREE** prior lines of therapy for their MM 3. **ANY** of the following ("a" to "e"): 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 e. Bendamustine will be used as triplet therapy in combination with both carfilzomib (Kyprolis) and dexamethasone	• 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/Sezary Syndrome	**ALL** of the following ("1", "2", and "3"): 1. Member has CD30+ disease 2. Bendamustine will be used in combination with brentuximab vedotin 3. **ONE** of the following disease types: a. Stage IVA2 non-Sezary disease b. Stage IVB visceral disease (solid organ) c. Generalized cutaneous or extracutaneous lesions with large cell transformation (LCT)	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 21-day or 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 or obinutuzumab (Gazyva)	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 21-day or 28-day cycle

	2. **ALL** of the following ("a", "b", and "c"): 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 c. Member has not been previously treated with bendamustine for their disease	
Nodular Lymphocyte-Predominant Hodgkin Lymphoma	**BOTH** of the following ("1" and "2") i. Bendamustine is being used as second-line or later therapy for relapsed, refractory or progressive disease ii. Bendamustine will be used in combination with rituximab	• 120 mg/m^2 given twice (e.g., days 1 and 2) of every 21-day or 28-day cycle
Pediatric Hodgkin Lymphoma	BOTH of the following ("1" and "2") 1. Bendamustine is being used as re-induction therapy or subsequent therapy for relapsed or refractory disease 2. Bendamustine will be used in combination with brentuximab vedotin	• 90 mg/m^2 given twice (e.g., days 1 and 2) during every 21-day cycle
Peripheral T-cell lymphoma (PTCL)	**ALL** of the following ("1", "2", and "3"): 1. Bendamustine will be used as a single agent 2. **EITHER** of the following ("i" or "ii"): i. Bendamustine will be used as initial palliative intent therapy ii. Bendamustine will be used as second-line or later therapy for relapsed/refractory disease 3. The member has **ANY** of the following disease subtypes: a. Anaplastic large cell lymphoma (ALCL) [including breast implant associated ALCL] b. Angioimmunoblastic T-cell lymphoma (AITL)	• 120 mg/m^2 given twice (e.g., days 1 and 2) during every 21-day or 28-day cycle

	c. Enteropathy-associated T-cell lymphoma (EATL) d. Follicular T-cell lymphoma (FTCL) e. Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) f. Nodal peripheral T-cell lymphoma with TFH phenotype (PTCL, TFH) g. Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)	
Post-Transplant Lymphoproliferative Disorder (PTLD)	**ALL** of the following ("1", "2", and "3"): 1. Treatment is used as second-line or later therapy, or as bridging therapy for members with intention to proceed to CAR T-cell therapy 2. Member has B-cell type, monomorphic PTLD 3. **ONE** of the following treatment regimens will be used: i. Bendamustine as a single agent ii. Bendamustine in combination with rituximab* iii. Bendamustine in combination with polatuzumab vedotin (with or without rituximab)	• 120 mg/m^2 given twice (e.g., days 1 and 2) during every 21-day or 28-day cycle
Splenic 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 medical therapy b. Bendamustine will be used combination with rituximab 2. **ALL** of the following ("a", "b", and "c"): a. Bendamustine is being used as second-line or later medical therapy for recurrent, 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

	c. Member has not been previously treated with bendamustine for their disease	
Systemic Light Chain Amyloidosis (SLCA)	**ALL** of the following ("1", "2", and "3"): 1. The diagnosis has been confirmed by the presence of amyloid deposits in tissue **AND** the deposits are composed of light chains 2. Bendamustine is being used as second-line or later therapy for relapsed/refractory disease 3. Bendamustine will be used in combination with dexamethasone	• 90 mg/m^2 given twice (e.g., days 1 and 2) during every 28-day cycle
Waldenström's macroglobulinemia (Including Bing Neel syndrome)	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
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 package insert) 2. Indication **AND** usage are recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation	• Dosage does not exceed the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guidelines for the diagnosis
**Obinutuzumab (Gazyva) may be substitute for rituximab in patients with intolerance (including those experiencing severe hypersensitivity reactions requiring discontinuation of rituximab) as well as 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 (except for hematopoietic cell transplantation conditioning regimen – approved for 2 doses only)		

Continuation of bendamustine **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1", "2", "3", and "4"):

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 (except for

hematopoietic cell transplantation conditioning regimen – see initiation criteria), **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. For brand Vivimusta (HCPCS - J9056) **ONLY** - **EITHER** of the following must apply ("a" or "b"):
    a. Member has a contraindication to **ALL** other available bendamustine products [Treanda and its generic equivalents (J9033), Bendeka (J9034), Belrapzo (J9036), bendamustine from Apotex (J9058), and bendamustine from Baxter (J9059)], **AND** the contraindication is not applicable to Vivimusta - the specific contraindication(s) and rationale for using Vivimusta must be provided
    b. Member has tried and had intolerable adverse effects to at least **TWO** other available bendamustine products [Treanda and its generic equivalents (J9033), Bendeka (J9034), Belrapzo (J9036), bendamustine from Apotex (J9058), and bendamustine from Baxter (J9059)], **AND** the intolerance is not expected to occur with Vivimusta - the specific intolerance(s) and rationale for using Vivimusta must be provided. Also, **BOTH** of the following are required:
        i. A completed MedWatch form (FDA 3500) must be submitted: https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda
        ii. A completed Naranjo Adverse Drug reaction probability scale must be submitted: https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf
4. 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), 20 minutes (for Vivimusta), or 10 minutes (for Bendeka) on days 1 and 2 of a 28 day cycle, up to 6 cycles	1. Hematologic toxicity a. Grade 3 or greater: reduce to 50 mg/m^2 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), 20 minutes (for Vivimusta), 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/m^2 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.
- Bendamustine (Apotex and Baxter) - 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 and generics - 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.

- Vivimusta - 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.

PRECAUTIONS:

Boxed Warning:

- None

Contraindications:

- Belrapzo - History of hypersensitivity reactions to bendamustine, polyethylene glycol 400, propylene glycol, or monothioglycerol.
- Bendamustine (Apotex) – Known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine, polyethylene glycol 400, absolute ethanol, sodium hydroxide and monothioglycerol.
- Bendamustine (Baxter) - A known hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine, polyethylene glycol 400, alcohol, or monothioglycerol.
- Bendeka - History of hypersensitivity reactions to bendamustine, polyethylene glycol 400, propylene glycol, or monothioglycerol.
- Treanda and generics - History of a hypersensitivity reaction to bendamustine.
- Vivimusta - History of a hypersensitivity reaction to bendamustine, polyethylene glycol 400, dehydrated alcohol, or monothioglycerol.

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.
- **Progressive Multifocal Leukoencephalopathy (PML):** Progressive multifocal leukoencephalopathy (PML), including fatal cases, have occurred following treatment with bendamustine, primarily in combination with rituximab or obinutuzumab. Monitor for new or worsening neurological, cognitive or behavioral signs or symptoms suggestive of PML.
- **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 and AP-rated generics)

J9033	Injection, bendamustine , 1 mg

HCPCS Coding (Bendeka)

J9034	Injection, bendamustine HCl (Bendeka), 1 mg

HCPCS Coding (Belrapzo)

J9036	Injection, bendamustine hydrochloride, (Belrapzo/bendamustine), 1 mg

HCPCS Coding (Vivimusta)

J9056	Injection, bendamustine hydrochloride (Vivimusta), 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity:

B20 [in combination with C83.30 – C83.39, C83.80 – C83.89, C83.90 – C83.99, C85.80 – C85.89]	Human immunodeficiency virus [HIV] disease [for AIDS-related B-cell lymphoma when billed in combination with another applicable code]
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
C82.50 – C82.59	Diffuse follicle center lymphoma
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 – C83.398	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
C84.00 – C84.09	Mycosis fungoides
C84.10 – C84.19	Sézary disease
C84.40 – C84.49	Peripheral T-cell lymphoma, not elsewhere classified
C84.60 – C84.69	Anaplastic large cell lymphoma, ALK-positive
C84.70 – C84.7A	Anaplastic large cell lymphoma, ALK-negative
C84.90 - C84.99	Mature T/NK-cell lymphomas, unspecified
C84.Z0 – C84.Z9	Other mature T/NK-cell lymphomas
C85.20 – C85.29	Mediastinal (thymic) large B-cell lymphoma
C85.80 – C85.89	Other specified types of non-Hodgkin lymphoma
C86.10	Hepatosplenic T-cell lymphoma not having achieved remission
C86.20	Enteropathy-type (intestinal) T-cell lymphoma not having achieved remission
C86.50	Angioimmunoblastic T-cell lymphoma not having achieved remission
C88.00	Waldenström macroglobulinemia not having achieved remission
C88.40	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma] not having achieved remission
C88.80	Other malignant immunoproliferative diseases not having achieved remission
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)
D59.12	Cold autoimmune hemolytic anemia
E85.81	Light chain (AL) amyloidosis
E85.89	Other amyloidosis
E85.9	Amyloidosis, unspecified
Z94.81	Bone marrow transplant status

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) or Local Coverage Determination (LCD) were found at the time of the last guideline review date. LCD ID number L33268 (BENDAMustine hydrochloride) was retired effective for services rendered on or after October 30, 2019.

DEFINITIONS:

None

RELATED GUIDELINES:

Bortezomib Injection, 09-J0000-92
Doxorubicin HCl Liposome (Doxil) Injection, 09-J0000-91
Ibrutinib (Imbruvica), 09-J2000-09
Obinutuzumab (Gazyva), 09-J2000-07
Oral Oncology Medications, 09-J3000-65
Rituximab Products, 09-J0000-59
Thalidomide (Thalomid) Capsules, 09-J1000-56

OTHER:

None.

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 07/10/24.

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.
03/15/20	Revision to the guideline including updates to the description section, position statement, and references based on new NCCN recommendations for various B-cell lymphomas.
08/15/20	Review and revision to guideline consisting of updating the position statement, billing/coding, related guidelines, and references.
08/15/21	Review and revision to guideline consisting of updating the position statement, precautions, billing/coding, related guidelines, and references.
10/01/21	Revision: New ICD-10 code C84.7A added.
08/15/22	Review and revision to guideline consisting of updating the position statement, billing/coding, and references.
10/01/22	Revision: ICD-10 code update.
02/15/23	Revision to guideline consisting of updating the description section, dosing/administration, precautions, billing/coding, and references related to the FDA approval of Vivimusta.
07/01/23	Revision: added HCPCS codes J9056, J9058, and J9059, and deleted code J9999.
08/15/23	Review and revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, and references. New indication of cold agglutinin disease. For MM, new triplet regimen of bendamustine + carfilzomib (Kyprolis) + dexamethasone. New 505(b)(2) bendamustine product information added.
08/15/24	Review and revision to guideline consisting of updating the description, position statement, billing/coding, and references. Per NCCN updates, revised the acceptable regimens for follicular and mantle cell lymphoma. For MM indication, added requirement that the member has received at least three prior lines of therapy. Added new indication of Mycosis Fungoides/Sezary Syndrome for use in certain situations. For brand Vivimusta (J9056), use is only permitted when other bendamustine products cannot be used.
10/01/24	Revision: ICD-10 code updates.
01/01/25	Revision: Deleted HCPCS codes J9058 and J9059. Revised code J9033. The bendamustine products from Apotex and Baxter are now included under code J9033.