**09-J0000-92**

**Original Effective Date: 04/15/09**

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**Revised: 07/15/19**

# Subject: Bortezomib 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:

Bortezomib (Velcade) is a small molecule, dipeptidyl boronic acid proteasome inhibitor. The 26S proteasome degrades ubiquitinated proteins and regulates the intracellular concentration of specific cell proteins and maintains cellular homeostasis. This disruption of homeostasis can lead to cell death. The first bortezomib product, Velcade, It was first approved by the US Food and Drug Administration (FDA) in May 2003 for treatment of persons with multiple myeloma (MM) who received at least two prior therapies and have demonstrated progression of the disease on the last therapy. It was the first proteasome inhibitor to be approved for MM, and over time it became a standard of care in MM combination drug regimens. Velcade also has orphan designations for the treatment of follicular non-Hodgkin's lymphoma (2011) and acute lymphoblastic leukemia (2015). Since initial approval, the use of bortezomib in other MM settings (e.g., primary therapy, maintenance therapy) is supported by referenced compendia, including National Comprehensive Cancer Network (NCCN). The FDA-approved indication was expanded to treatment of MM patients who have received at least one prior therapy in May 2005, and then to first-line treatment of MM in June 2008. In December 2006, the FDA granted approval for treatment of refractory or recurrent mantle cell lymphoma (MCL), a rare form of B-cell non-Hodgkin's lymphoma (NHL). The indication was expanded to first-line treatment of MCL in October 2014. In November 2017 the FDA approved an additional bortezomib product (manufactured by Fresenius Kabi). The product is not a true generic to Velcade since it was approved via a new drug application (NDA). As such, there are differences in the FDA-approved indications (i.e., Velcade is approved for first-line use in MCL while bortezomib is approved for second-line use in MCL); the approved routes of administration (i.e., Velcade is approved for both IV and subcutaneous use while bortezomib is only approved for IV use; and the product formulations (i.e., Velcade contains mannitol while bortezomib contains glycine). In addition to use in MM and MCL, the NCCN guidelines support bortezomib therapy for treatment of adult T-Cell

leukemia/lymphoma, multicentric Castleman's disease, systemic light chain amyloidosis, and Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma.

## POSITION STATEMENT:

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

1. Bortezomib is used for **ANY** indication listed in Table 1, and **ALL** indication-specific criteria are met.
2. Bortezomib will **NOT** be used in combination with another proteasome inhibitor [e.g., carfilzomib (Kyprolis) or ixazomib (Ninlaro)].
3. The dosage of bortezomib given intravenously (or subcutaneously if brand Velcade) does not exceed **EITHER** of the following:
   a. 1.3 mg/m$^2$ twice weekly for 14 days (4 doses) of a 21-day cycle (e.g., days 1, 4, 8, and 11)
   b. 1.6 mg/m$^2$ once weekly for 28 days (4 doses) of a 28-day or 35-day cycle (e.g., days 1, 8, 15, and 22)

### Table 1

| **Indications and Specific Criteria** | |
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| **Indication** | **Criteria** |
| Adult T-Cell Leukemia/Lymphoma (ATLL) [a type of cutaneous CD30+ T-Cell lymphoproliferative disorder] | **ALL** of the following ("1", "2", and "3"):<br>1. Bortezomib will be used as second-line or later therapy for relapsed or refractory disease<br>2. Member has the acute or lymphoma disease subtype (as opposed to the chronic/smoldering disease subtype)<br>3. Bortezomib will be used as monotherapy |
| Lymphoplasmacytic lymphoma | **BOTH** of the following ("1" and "2"):<br>1. Member is symptomatic (e.g., hyperviscosity, neuropathy, symptomatic adenopathy or organomegaly, amyloidosis, cryoglobulinemia, cold agglutinin disease, presence of cytopenia)<br>2. One of the following regimens will be used ("a", "b", "c", or "d"):<br>a. Bortezomib monotherapy<br>b. Bortezomib + dexamethasone<br>c. Bortezomib + rituximab<br>d. Bortezomib + rituximab + dexamethasone |
| Mantle cell lymphoma (MCL) | **BOTH** of the following ("1" and "2"):<br>1. The diagnosis has been confirmed by tissue biopsy with |

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| | appropriate histology and immunophenotyping<br>2. Bortezomib will be used in **EITHER** of the following settings ("a" or "b"):<br>a. Less aggressive induction therapy as part of the VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone) regimen<br>b. Second-line or later therapy with or without rituximab for relapsed, refractory, or progressive disease |
| Multicentric Castleman's disease (CD) | **BOTH** of the following ("1" and "2"):<br>1. Bortezomib will be used as subsequent therapy for disease that has progressed following treatment of relapsed/refractory or progressive disease (i.e., third-line or later treatment)<br>2. Bortezomib will be used as either monotherapy or in combination with rituximab (Rituxan) |
| Multiple myeloma (MM) | **BOTH** of the following ("1" and "2"):<br>1. Member has active (symptomatic) multiple myeloma<br>2. The member's baseline (i.e., within 90 days prior to initiating treatment with bortezomib) serum monoclonal protein (M-protein) level, as detected by serum protein electrophoresis (SPEP), is provided*<br>**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* |
| Systemic light chain amyloidosis | **ALL** of the following ("1", "2", and "3"):<br>1. The diagnosis has been confirmed by the presence of amyloid deposits in tissue **AND** the deposits are composed of light chains<br>2. The member's baseline (i.e., within 90 days prior to initiating treatment with bortezomib) serum free light chains (SFLC) levels (kappa and lambda), as detected by serum free light chain assay (SFLCA), is provided<br>3. One of the following regimens will be used ("a", "b", "c", or "d"):<br>a. Bortezomib monotherapy<br>b. Bortezomib + dexamethasone<br>c. Bortezomib + cyclophosphamide + dexamethasone<br>d. Bortezomib + melphalan + dexamethasone |

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| Waldenström's macroglobulinemia | **ALL** of the following ("1", "2", and "3"):<br><br>1. Member is symptomatic (e.g., hyperviscosity, neuropathy, symptomatic adenopathy or organomegaly, amyloidosis, cryoglobulinemia, cold agglutinin disease, presence of cytopenia)<br>2. The member's baseline (i.e., within 90 days prior to initiating treatment with bortezomib) serum IgM level is provided<br>3. One of the following regimens will be used ("a", "b", "c", or "d"):<br>a. Bortezomib monotherapy<br>b. Bortezomib + dexamethasone<br>c. Bortezomib + rituximab<br>d. Bortezomib + rituximab + dexamethasone |
| Other FDA-approved or NCCN supported diagnosis (not previously listed above and not an orphan indication) | **EITHER** of the following ("1" or "2"):<br><br>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)<br>2. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation |
| **Duration of approval**: 6 months | |

Continuation of bortezomib injection **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "4"):

1. Authorization or reauthorization for bortezomib has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of any indications listed in Table 1, **OR** the member previously met **ALL** indication-specific initiation criteria
2. Documentation of a favorable response to treatment is provided (see indication-specific criteria below):
    a. ATLL, multicentric Castleman's disease, lymphoplasmacytic lymphoma, mantle cell lymphoma,Waldenström's macroglobulinemia, or other FDA-approved or NCCN-supported diagnosis: provider attestation that the member had not had disease progression during bortezomib treatment
    b. Multiple myeloma:
        i. If less than18 months of treatment – a serum M-protein level decrease of 25% or more* compared to baseline, or M-protein is undetectable, **AND** no increase in the size or number of lytic bone lesions after at least two cycles of treatment with bortezomib[†,#]
        ii. If 18 or more months of treatment - provider attestation that the member had not had disease progression during bortezomib treatment

**If the M-protein was undetectable by SPEP at baseline and a baseline SFLC level is available, a decrease of 25% or more in the difference between the light chain produced by the myeloma cells (lambda or kappa) and the other light chain must be achieved*

*[†]If the M-protein was undetectable by SPEP at baseline and a baseline SFLC level is available, a follow-up SFLC level must be submitted*

*[#]An exception is permitted if a baseline M-protein AND SFLCA are unavailable. In these cases the physician may provide an attestation of a beneficial clinical response which must include no increase in the size or number of lytic bone lesions.*

c. Systemic light chain amyloidosis:
   i. If less than18 months of treatment - there has been a reduction (improvement) in the member's SFLC level as compared to baseline[¥] after at least two cycles of treatment with bortezomib
   ii. If 18 or more months of treatment - provider attestation that the member had not had disease progression during bortezomib treatment

   *[¥]An exception is permitted if a baseline SFLC value is unavailable. A follow-up SFLC level still must be submitted. The physician must also provide an attestation of a beneficial clinical response.*

3. Bortezomib will **NOT** be used in combination with another proteasome inhibitor [e.g., carfilzomib (Kyprolis) or ixazomib (Ninlaro)].
4. The dosage of bortezomib does not exceed **EITHER** of the following:
   a. 1.3 mg/m$^2$ twice weekly for 14 days (4 doses) of a 21-day cycle (e.g., days 1, 4, 8, and 11)
   b. 1.6 mg/m$^2$ once weekly for 28 days (4 doses) of a 28-day or 35-day cycle (e.g., days 1, 8, 15, and 22)

**Duration of approval**: 1 year

Bortezomib injection **meets the definition of medical necessity** when: (1) administered for **EITHER** of the following orphan indications, (2) it will **NOT** be used in combination with another proteasome inhibitor [e.g., carfilzomib (Kyprolis) or ixazomib (Ninlaro)], **AND** (3) the dosage does not exceed 1.3 mg/m$^2$ twice weekly for 14 days (4 doses) of a 21-day cycle **OR** 1.6 mg/m2 once weekly for 28 days (4 doses) of a 28-day or 35-day cycle (e.g., days 1, 8, 15, and 22):

1. Acute lymphoblastic leukemia (ALL)
2. Follicular non-Hodgkin lymphoma (NHL)

**Duration of approval**: 1 year

## 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:**

- Velcade - indicated for the treatment of patients with multiple myeloma and the treatment of patients with mantle cell lymphoma. The recommended dose is 1.3 mg/$m^2$ either as a 3 to 5 second bolus intravenous injection or subcutaneous injection. The frequency of administration is dependent on the indication for therapy. See the package insert for specific dosage recommendations.
- Bortezomib (Fresenius Kabi) - indicated for the treatment of patients with multiple myeloma and the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy. The recommended dose is 1.3 mg/m2 administered as a 3 to 5 second bolus intravenous injection. For intravenous use only. The frequency of administration is dependent on the indication for therapy. See the package insert for specific dosage recommendations.

**Dosage Modifications:** See the package insert for specific dosage adjustments based on toxicity. No dosage adjustment is needed in patients with renal impairment. The exposure of bortezomib is increased in patients with moderate (bilirubin ≥1.5 to 3-times the ULN) and severe (bilirubin >3-times the ULN) hepatic impairment, and the starting dose should be reduced.

**Drug Availability:**

- Velcade is supplied as a single-use vial containing 3.5 mg of bortezomib as lyophilized powder. Each route of administration (i.e., IV or SQ) has a different reconstitution concentration and caution should be used when calculating the volume to be administered.
- Bortezomib (Fresenius Kabi) is supplied in a 10 mL vial containing 3.5 mg of bortezomib as a white to off-white cake or powder in a single-dose vial for reconstitution (after reconstitution the solution is clear and colorless).

## PRECAUTIONS:

**Contraindications:**

- **Velcade** - Patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol.
- **Bortezomib (Fresenius Kabi)** - Patients with hypersensitivity (not including local reactions) to bortezomib, boron, boric acid or glycine
- **Both products** - Intrathecal administration is contraindicated. Fatal events have occurred with intrathecal administration.

**Warnings/Precautions:**

- **Cardiac toxicity**: worsening of and development of cardiac failure has occurred. Closely monitor persons with existing disease or risk factors for heart disease.
- **Hepatic toxicity**: Acute liver failure has been reported in persons receiving multiple concurrent medications and with serious underlying medical conditions. Monitor hepatic enzymes during treatment.
- **Hypotension**: use caution when treating members prescribed antihypertensive medications, with a history of syncope, or with dehydration as this can result in increased risk of orthostatic and postural hypotension.
- **Pulmonary toxicity**: acute respiratory syndromes have occurred; monitor closely for new or worsening symptoms.
- **Gastrointestinal toxicity**: nausea, diarrhea, constipation and vomiting may require use of antiemetic and antidiarrheal medications or fluid replacement.

- **Peripheral neuropathy**: new onset or exacerbation of pre-existing peripheral neuropathy may occur; managed with dose modification or discontinuation.
- **Posterior Reversible Encephalopathy Syndrome (PRES)**: consider MRI imaging for onset of visual or neurological symptoms; discontinue bortezomib therapy in persons developing PRES.
- **Thrombocytopenia and neutropenia**: monitor complete blood counts regularly throughout treatment.
- **Tumor lysis syndrome may occur**. Closely monitor members with a high tumor burden.
- **Embryo-fetal Toxicity**: may cause embryo-fetal harm. Women should avoid becoming pregnant while being treated with bortezomib. Advise females and males of reproductive potential that they must use contraception during treatment with bortezomib and for 2 months following treatment.
- **Diabetes**: patients with diabetes may require close monitoring of blood glucose and adjustment of anti-diabetic medication.
- **Drug interactions**: co-administration with strong CYP3A4 inhibitors can increase bortezomib exposure; closely monitor. Co-administration with strong CYP3A4 inducers can decrease bortezomib exposure; avoid concomitant use.

## BILLING/CODING INFORMATION:

The following codes may be used to describe:

### HCPCS Coding:

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| J9041 | Injection, bortezomib (Velcade), 0.1 mg |
| J9044 | Injection, bortezomib, not otherwise specified, 0.1 mg |

### ICD-10 Diagnoses Codes That Support Medical Necessity:

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| C82.00 – C82.99 | Follicular lymphoma |
| C83.00 – C83.09 | Small cell B-cell lymphoma |
| C83.10 – C83.19 | Mantle cell lymphoma |
| C88.0 | Waldenstrom macroglobulinemia |
| C90.00 – C90.02 | Multiple myeloma |
| C90.10 – C90.12 | Plasma cell leukemia |
| C90.20 – C90.22 | Extramedullary plasmacytoma |
| C90.30 - C90.32 | Solitary plasmacytoma |
| C91.00 – C91.02 | Acute lymphoblastic leukemia [ALL] |
| 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 |
| D36.0 | Benign neoplasm of lymph nodes |
| D47.Z2 | Castleman disease |
| E85.81 | Light chain (AL) amyloidosis |
| E85.89 | Other amyloidosis |
| E85.9 | Amyloidosis, unspecified |
| R59.0 - R59.9 | Enlarged lymph nodes |

## 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 revised date. The following Local Coverage Determination (LCD) was reviewed on the last guideline review date: Bortezomib (Velcade), (L33273) located at fcso.com.

## DEFINITIONS:

**Heavy chain** – the larger component of an immunoglobulin. There are five types: IgG, IgA, IgM, IgD, and IgE.

**Immunoglobulins (a.k.a., antibodies)** – proteins made by normal plasma cells that have an important role in fighting infection as part of the humoral immune response. Antibodies are composed of two heavy chains and two light chains that form a larger complex. Each plasma cell produces only one type of heavy chain and one type of light chain.

**Light chain** – the smaller component of an immunoglobulin. There are two types: kappa and lambda.

**Myeloma Protein (M-Protein)** – a nonfunctional immunoglobulin protein or protein fragment produced by malignant plasma cells (or myeloma cells). Since myeloma cells are monoclonal, the M-proteins for a given patient are structurally identical. Both portions of an immunoglobulin (the heavy chain and light chain) can be found in the serum, while only light chains can be found in the urine.

**Plasma cell** - a fully differentiated B lymphocyte (a type of white blood cell) that is specialized for immunoglobulin production and is found primarily in bone marrow.

**Primary refractory MM** - patients who never achieve at least a MR to initial induction therapy and progress while on therapy

**Progressive MM** - at least a 25% increase from nadir in the serum M-protein (absolute increase must be ≥0.5 g/dL) or urine M-protein (absolute increase must be ≥200mg/24 hours), or in the difference between involved and uninvolved serum-free light-chain (FLC) levels (with an abnormal FLC ratio and FLC difference >100 mg/L).

**Relapsed and refractory MM** - patients who never achieve at least a MR or who progress within 60 days of their last therapy

**Serum Protein Electrophoresis (SPEP)** – a test that detects and quantifies the amount of M-protein in the serum. An serum M-protein of greater than 30 g/L is consistent with a diagnosis of MM.

**Smoldering (Asymptomatic) myeloma:** defined as M-protein in serum of 30 g/dL or more and/or bone marrow clonal plasma cells of 10% or more, but no related organ or tissue impairment (no end organ damage, including bone lesions) or symptoms.

## RELATED GUIDELINES:

**Allogeneic Bone Marrow and Stem Cell Transplantation, 02-38240-01**

**Carboplatin (Paraplatin) IV, 09-J0000-93**

**Carfilzomib (Kyprolis) IV, 09-J1000-81**

**Daratumumab (Darzalex) IV, 09-J2000-49**

**Doxorubicin HCl Liposome (Doxil) IV, 09-J0000-91**

**Elotuzumab (Empliciti) IV, 09-J2000-50**

**Interferons for Oncology Use, 09-J1000-37**

**Ixazomib (Ninlaro), 09-J2000-51**

**Lenalidomide (Revlimid), 09-J0000-80**

**Panobinostat (Farydak), 09-J2000-37**

**Pomalidomide (Pomalyst) Capsule, 09-J1000-95**

**Thalidomide (Thalomid) Capsules, 09-J1000-56**

## OTHER:

None applicable.

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## COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 06/12/19.

## GUIDELINE UPDATE INFORMATION:

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| 04/15/09 | New Medical Coverage Guideline. |
| 10/15/09 | Revision; consisting of clarifying dosage and updating coding. |
| 07/15/10 | Review and revision; consisting of updating references. |
| 08/01/10 | Revision; consisting of updating coding. |
| 02/01/11 | Revision; consisting of updating coding. |
| 02/15/11 | Revision; consisting of adding ICD-10 codes. |
| 07/15/11 | Review and revision to guideline; consisting of updating coding and references. |
| 07/15/12 | Review and revision to guideline; consisting of updating coding, references and exceptions. |
| 12/15/12 | Revision to guideline; consisting of updating coding. |
| 07/15/13 | Review and revision to guideline; consisting of revising position statement to include updated NCCN category 1 and 2A recommendations; reformatting/revising dosage/administration, precautions, program exceptions, and description section; updating references and coding. |
| 12/15/13 | Revision to guideline; consisting of revising medical necessity criteria for coverage of mantle cell lymphoma. |
| 07/15/14 | Review and revision to guideline; consisting of revising position statement, updating references and coding. |
| 12/15/14 | Revision to guideline; consisting of position statement, dosing/administration. |
| 07/15/15 | Review and revision to guideline; consisting of updating description, position statement, dosage/administration, precautions, coding/billing, and references. |

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| 10/01/15 | Revision consisting of update to Program Exceptions section. |
| 11/01/15 | Revision: ICD-9 Codes deleted. |
| 07/15/16 | Review and revision to guideline consisting of updating position statement, billing/coding information, definitions, related guidelines, and references. |
| 10/01/16 | Revision: ICD-10 code updates. |
| 02/16/17 | Revision: Update to Position Statement. |
| 07/15/17 | Review and revision to guidelines consisting of updating the description section, position statement, and references. |
| 03/15/18 | Revision to guidelines consisting of updating description, position statement, dosage/administration, precautions, coding/billing, and references based on a newly approved bortezomib product manufactured by Fresenius Kabi. |
| 07/15/18 | Review and revision to guidelines consisting of updating the description section, position statement, billing/coding information, and references. |
| 01/01/19 | Revision: HCPCS code updates. Added J9044 and removed J9999. Modified J9041 description. |
| 07/15/19 | Review and revision to guidelines consisting of updating the description section, position statement, billing/coding information, and references. |