Bortezomib*
(Intravenous Only)

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I. Length of Authorization [1,2,6,9,15,26,27,36-42]

Coverage will be provided for 6 months and may be renewed unless otherwise specified.

- Initial treatment for Multiple Myeloma: Coverage will be provided for a total of 9 cycles (42-days per cycle).
- Re-treatment of Multiple Myeloma, initial treatment of Mantle Cell Lymphoma, & Adult T-Cell Leukemia/Lymphoma: Coverage will be provided for a total of 8 cycles (21-days per cycle).
- Systemic Light Chain Amyloidosis as a single agent or in combination with cyclophosphamide and/or dexamethasone: Coverage will be provided for a total of 8 cycles (35-days per cycle as a single agent; 21- or 28-days per cycle in combination with cyclophosphamide and/or dexamethasone).
- Systemic Light Chain Amyloidosis in combination with melphalan and dexamethasone: Coverage will be provided for a total of 9 cycles (21-days per cycle)
- Waldenström's Macroglobulinemia in combination with rituximab and/or dexamethasone: Coverage will be provided for a total of 6 cycles (28-days per cycle) or 8 cycles (21-days per cycle).

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Bortezomib 3.5 mg powder for injection: 8 vials per 28 day supply

B. Max Units (per dose and over time) [HCPCS Unit]:

- **Multiple Myeloma (maintenance therapy for transplant ineligible patients) & Systemic Light Chain Amyloidosis:**
  - 280 billable units every 35 days
- **AIDS-Related Kaposi Sarcoma & Waldenström's Macroglobulinemia:**
  - 280 billable units every 28 days

- **Multiple Myeloma (initial treatment):**
  - 140 billable units every 42 days
- **All Other Indications:**
  - 140 billable units every 21 days

III. Initial Approval Criteria [1,2,3]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age (unless otherwise specified); **AND**

Universal Criteria [1,2]

- Will not be administered intrathecally; **AND**

Multiple Myeloma † [1-6,14,16-21,25-27]

- Used in combination with a corticosteroid-containing regimen as primary therapy for symptomatic disease or for relapse (re-treatment) after 6 months following primary induction therapy with the same regimen; **OR**
- Used as maintenance therapy as a single agent or in combination with lenalidomide; **OR**
- Used for relapsed or progressive disease in combination with a dexamethasone-containing regimen

Mantle Cell Lymphoma – B-Cell Lymphoma † [1,2,3,13,22-24,28]

- Used as induction therapy; **AND**
  - Used as a component of VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone); **OR**
- Used as second-line therapy; **AND**
  - Used as a single agent; **OR**
  - Used in combination with rituximab; **OR**
  - Used as a component of VR-CAP in patients with a partial response with intention to proceed to transplant

Systemic Light Chain Amyloidosis ‡ [3,11]

- Patient has newly diagnosed disease OR used as repeat initial therapy if relapse-free for several years; **AND**
  - Used in combination with cyclophosphamide and dexamethasone; **OR**
  - Used as a single agent; **OR**
  - Used in combination with dexamethasone with or without melphalan
- Patient has relapsed or refractory disease; **AND**
  - Used as a single agent; **OR**
  - Used in combination with dexamethasone with or without melphalan

Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma ‡ [3,6,12,15,30]

- Used in combination with dexamethasone and rituximab; **OR**
- Used as a single agent; **OR**
- Used in combination with rituximab; **OR**
- Used in combination with dexamethasone

Multicentric Castleman's Disease – B-Cell Lymphoma ‡ [3,13]

- Used as subsequent therapy; **AND**
- Patient has progressed following treatment for relapsed/refractory or progressive disease; **AND**
- Used as a single agent or in combination with rituximab

Adult T-Cell Leukemia/Lymphoma ‡ [3,8,10,38]

- Used as a single agent; **AND**
- Used as subsequent therapy for non-responders to first-line therapy for acute disease or lymphoma subtypes

Pediatric Acute Lymphoblastic Leukemia ‡ [3,9,29]

- Patient is at least 1 year of age; **AND**
  - Patient has relapsed or refractory B-cell disease (B-ALL); **AND**
    - Used as a component of the COG AALL07P1 regimen (bortezomib, vincristine, doxorubicin, pegaspargase, prednisone); **AND**
      - Patient has Philadelphia (Ph) chromosome negative disease; **OR**
      - Used in combination with dasatinib or imatinib for Philadelphia (Ph) chromosome positive disease; **OR**
  - Patient has relapsed or refractory T-cell disease (T-ALL); **AND**
    - Used in combination with a corticosteroid (e.g., prednisone or dexamethasone), vincristine, doxorubicin, and pegaspargase

AIDS-Related Kaposi Sarcoma ‡ [3,42]

- Used as subsequent therapy in combination with antiretroviral therapy (ART); **AND**
- Patient has relapsed/refractory advanced, cutaneous, oral, visceral, or nodal disease; **AND**
- Patient has progressed on or not responded to first-line therapy; **AND**
- Patient has progressed on alternate first-line therapy

**Bortezomib was approved by the FDA as a 505(b) (2) NDA of the innovator product, Velcade (bortezomib) for Injection, for intravenous use only and thus should NOT be considered therapeutically interchangeable (i.e. not suitable for substitution) for other non-approved indications.*

† FDA Approved Indication(s); ‡ Compendia recommended indication(s)

IV. Renewal Criteria [1,2,7]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Example of unacceptable toxicity include peripheral neuropathy, hypotension, cardiac toxicity, pulmonary toxicity, posterior reversible encephalopathy syndrome (PRES), gastrointestinal toxicity, thrombocytopenia, neutropenia, tumor lysis syndrome, hepatic toxicity, thrombotic microangiopathy, etc.

V. Dosage/Administration [1,2,6,7,9,15,26,27,31,36-43]

Indication	Dose
Multiple Myeloma – previously untreated	1.3 mg/m² intravenously (IV) in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles. In cycles 1-4, bortezomib is given twice weekly (days 1, 4, 8, 11, 22, 25, 29, and 32). In cycles 5-9, bortezomib is given once weekly (days 1, 8, 22, and 29).
Multiple Myeloma – maintenance therapy	Following primary therapy with a bortezomib-containing regimen for transplant-ineligible patients: 1.6 mg/m² IV weekly (days 1, 8, 15, and 22) every 35 days until disease progression or unacceptable toxicity Following autologous stem cell transplant: 1.3 mg/m² IV every two weeks until disease progression or unacceptable toxicity
Multiple Myeloma – re-treatment	1.3 mg/m² IV twice weekly (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21) for up to 8 cycles
Mantle Cell Lymphoma – previously untreated	1.3 mg/m² IV in combination with rituximab, cyclophosphamide, doxorubicin, and oral prednisone for six 3-week treatment cycles. Bortezomib is given twice weekly (days 1, 4, 8, and 11) followed by a 10-day rest period on days 12-21. For patients with a response first documented at cycle 6, two additional cycles are recommended.
Multiple Myeloma & Mantle Cell Lymphoma – relapsed	1.3 mg/m² IV twice weekly (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21) • For extended therapy of more than 8 cycles, bortezomib may be administered on the standard schedule or, for relapsed multiple myeloma, on a maintenance schedule of once weekly for 4 weeks (days 1, 8, 15, and 22), followed by a 13-day rest period (days 23 to 35).
Systemic Light Chain Amyloidosis	Single agent: 1.6 mg/m² IV weekly (days 1, 8, 15, and 22) every 35 days for up to 8 cycles

	<u>In combination with cyclophosphamide and/or dexamethasone:</u> 1.3 mg/m² IV twice weekly (days 1, 4, 8, and 11) every 21 or 28 days for up to 8 cycles <u>In combination with melphalan and dexamethasone:</u> 1.3mg/m² IV twice weekly (days 1, 4, 8, and 11) every 28 days for up to 9 cycles
Waldenström's Macroglobulinemia	<u>Single agent:</u> • 1.3 mg/m² IV twice weekly (days 1, 4, 8, and 11) every 21 days, until disease progression or unacceptable toxicity <u>In combination with rituximab and/or dexamethasone:</u> • 1.3 mg/m² IV twice weekly (days 1, 4, 8, and 11) every 21 days for 4 continuous cycles, followed by a 12-week rest period, then up to 4 additional cycles given every 12 weeks • 1.6 mg/m² IV weekly (days 1, 8, 15, and 22) every 28 days for up to 6 cycles
Adult T-Cell Leukemia/ Lymphoma	1.3 mg/m² IV twice weekly (days 1, 4, 8, and 11) every 21 days for up to 8 cycles
AIDS-Related Kaposi Sarcoma	1.6 mg/m² IV weekly (days 1, 8, and 15) every 28 days
All Other Indications	1.3 mg/m² IV twice weekly (days 1, 4, 8, and 11) every 21 days

VI. Billing Code/Availability Information

<u>HCPCS Code</u>:

- J9044 – Injection, bortezomib, not otherwise specified, 0.1 mg; 1 billable unit = 0.1 mg

<u>NDC(s)</u>:

- Bortezomib 3.5 mg single-use vial powder for injection: 63323-0721-xx (Fresenius Kabi)
- Bortezomib 3.5 mg single-use vial powder for injection: 43598-0865-xx (Dr. Reddy's Laboratories)

VII. References

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3. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Bortezomib. National Comprehensive Cancer Network, 2020. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most

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11. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Systemic Light Chain Amyloidosis. Version 1.2020. National Comprehensive Cancer Network, 2020. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed July 2020.
12. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma. Version 2.2020. National Comprehensive Cancer Network, 2020. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER

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Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C46.0	Kaposi's sarcoma of skin
C46.1	Kaposi's sarcoma of soft tissue
C46.2	Kaposi's sarcoma of palate
C46.3	Kaposi's sarcoma of lymph nodes
C46.4	Kaposi's sarcoma of gastrointestinal sites
C46.50	Kaposi's sarcoma of unspecified lung
C46.51	Kaposi's sarcoma of right lung
C46.52	Kaposi's sarcoma of left lung
C46.7	Kaposi's sarcoma of other sites
C46.9	Kaposi's sarcoma, unspecified
C83.00	Small cell B-cell lymphoma, unspecified site
C83.01	Small cell B-cell lymphoma, lymph nodes of head, face and neck
C83.02	Small cell B-cell lymphoma, intrathoracic lymph nodes
C83.03	Small cell B-cell lymphoma, intra-abdominal lymph nodes
C83.04	Small cell B-cell lymphoma, lymph nodes of axilla and upper limb
C83.05	Small cell B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.06	Small cell B-cell lymphoma, intrapelvic lymph nodes
C83.07	Small cell B-cell lymphoma, spleen
C83.08	Small cell B-cell lymphoma, lymph nodes of multiple sites
C83.09	Small cell B-cell lymphoma, extranodal and solid organ sites
C83.10	Mantle cell lymphoma, unspecified site
C83.11	Mantle cell lymphoma, lymph nodes of head, face and neck
C83.12	Mantle cell lymphoma, intrathoracic lymph nodes
C83.13	Mantle cell lymphoma, intra-abdominal lymph nodes
C83.14	Mantle cell lymphoma, lymph nodes of axilla and upper limb
C83.15	Mantle cell lymphoma, lymph nodes of inguinal region and lower limb
C83.16	Mantle cell lymphoma, intrapelvic lymph nodes
C83.17	Mantle cell lymphoma, spleen
C83.18	Mantle cell lymphoma, lymph nodes of multiple sites
C83.19	Mantle cell lymphoma, extranodal and solid organ sites
C88.0	Waldenstrom macroglobulinemia
C90.00	Multiple myeloma not having achieved remission
C90.01	Multiple myeloma in remission

ICD-10	ICD-10 Description
C90.02	Multiple myeloma, in relapse
C90.10	Plasma cell leukemia not having achieved remission
C90.11	Plasma cell leukemia in remission
C90.12	Plasma cell leukemia in relapse
C90.20	Extramedullary plasmacytoma not having achieved remission
C90.21	Extramedullary plasmacytoma in remission
C90.22	Extramedullary plasmacytoma in relapse
C90.30	Solitary plasmacytoma not having achieved remission
C90.31	Solitary plasmacytoma in remission
C90.32	Solitary plasmacytoma in relapse
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.02	Acute lymphoblastic leukemia, 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
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	Localized enlarged lymph nodes
R59.1	Generalized enlarged lymph nodes
R59.9	Enlarged lymph nodes, unspecified
Z85.72	Personal history of non-Hodgkin lymphomas
Z85.79	Personal history of other malignant neoplasms of lymphoid, hematopoietic and related tissues

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA):

Jurisdiction(s): 6 & K	**NCD/LCD/LCA Document (s):** A52371
https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A52371&bc=gAAAAAAAAAAAAA	

Jurisdiction(s): J & M	**NCD/LCD/LCA Document (s):** A56141
https://www.cms.gov/medicare-coverage-database/search/lcd-date-search.aspx?DocID=A56141&bc=gAAAAAAAAAAA	

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC