Bortezomib (Velcade®)

NDC CODE(S) 63020-0049-XX VELCADE 3.5MG Solution Reconstituted (MILLENNIUM PHARMACEUTICALS)

DESCRIPTION

Bortezomib, initially produced under the trade name Velcade, is the first antineoplastic agent to target the proteasome, a large intracellular cytoplasmic organelle responsible for the majority of protein degradation in mammalian cells. Proteins are tagged for destruction when conjugated to ubiquitin. They then enter the proteasome and are degraded via the ubiquitin-proteasome pathway. This pathway is central to cellular homeostasis, playing an essential role in the cell cycle, cellular proliferation and apoptosis.

Bortezomib, a boron-containing molecule, reversibly inhibits the ubiquitin-proteasome pathway resulting in cell-cycle arrest and apoptosis. It has been shown in vitro to be cytotoxic to a variety of cancer cells and in vivo causes a delay in tumor growth

POLICY

- Bortezomib for the treatment of the following is considered ***medically necessary*** if the medical appropriateness criteria are met: **(See Medical Appropriateness below.)**
  - Adult T-Cell Leukemia/Lymphoma
  - Kaposi Sarcoma
  - Mantle cell lymphoma
  - Multicentric Castleman's Disease
  - Multiple myeloma
  - Pediatric Acute Lymphoblastic Leukemia
  - Pediatric Hodgkin Lymphoma
  - Systemic Light Chain Amyloidosis
  - Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma
- Bortezomib for the treatment of other conditions/diseases is considered ***investigational.***

MEDICAL APPROPRIATENESS

INITIAL APPROVAL CRITERIA

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

Universal Criteria

Will not be administered intrathecally; **AND**

Multiple Myeloma

- 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; **OR**
- Used in combination with dexamethasone in patients with a confirmed diagnosis of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) Syndrome

Mantle Cell Lymphoma – B-Cell Lymphoma

- Used as induction or additional therapy; **AND**
  - Used as a component of VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone); **OR**
- Used as subsequent therapy; **AND**
  - Used as a single agent; **OR**
  - ~~o~~ Used in combination with rituximab

Systemic Light Chain Amyloidosis

- 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 or lenalidomide; **OR**
  - Used in combination with daratumumab and hyaluronidase-fihj, cyclophosphamide, and dexamethasone; **OR**
- 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

- 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

- 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

- 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

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

** Pediatric patients may include certain adolescent and young adult (AYA) patients up to 30 years of age.*

Kaposi Sarcoma

- Used as subsequent therapy in combination with antiretroviral therapy (ART) for relapsed or refractory disease; **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; **AND**
  - Used as a single-agent in patients without human immunodeficiency virus (HIV); **OR**
  - Used in combination with antiretroviral therapy (ART) for patients with HIV

Pediatric Hodgkin Lymphoma

- Patient age is 18 years and under*; AND
- Used for relapsed or refractory disease in combination with ifosfamide and vinorelbine

** Pediatric Hodgkin Lymphoma patients may include certain adolescent and young adult (AYA) patients up to 39 years of age.*

RENEWAL 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 Initial Approval Criteria; **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.

DOSAGE/ADMINISTRATION

INDICATION	DOSE
Multiple Myeloma – Initial treatment	1.3 mg/m2 intravenously (IV) /subcutaneously (SC) 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: 1.3 mg/m² IV/SC every two weeks or 1.6 mg/m2 IV/SC 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/SC every two weeks until disease progression or unacceptable toxicity

Multiple Myeloma – re-treatment	1.3 mg/m² IV/SC 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 IVSC 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/SC 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 IVSC weekly (days 1, 8, 15, and 22) every 35 days or 1.3 mg/m² IV/SC twice weekly (days 1, 4, 8, and 11) every 21 days for up to 8 cycles In combination with cyclophosphamide and/or dexamethasone: 1.3 mg/m² IV /SC twice weekly (days 1, 4, 8, and 11) every 21 or 28 days for up to 8 cycles In combination with melphalan and dexamethasone: 1.3mg/m2 IV/SC twice weekly (days 1, 4, 8, and 11) every 28 days for up to 9 cycles In combination with lenalidomide and dexamethasone: 1.3mg/m2 IV/SC twice weekly (days 1, 8, and 15) every 28 days for up to 8 cycles In combination with daratumumab and hyaluronidase-fihj, cyclophosphamide, and dexamethasone: 1.3mg/m2 IV/SC weekly (days 1, 8, 15, and 22) every 28 days for up to 2 years
Waldenström's Macroglobulinemia	Single agent: • 1.3 mg/m² IV/SC twice weekly (days 1, 4, 8, and 11) every 21 days, until disease progression or unacceptable toxicity In combination with rituximab and/or dexamethasone: • 1.3 mg/m² IV/SC 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/SC weekly (days 1, 8, and 15, and 22) every 28 days for up to 6 cycles
Adult T-Cell Leukemia/ Lymphoma	1.3 mg/m² IV/SC 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
Pediatric Hodgkin Lymphoma	1.2 mg/m2 IV/SC on days 1, 4, and 8 every 21 days for up to 4 cycles
All Other Indications	1.3 mg/m² IV/SC twice weekly (days 1, 4, 8, and 11) every 21 days
Reconstituted concentration varies by route of administration: • *1 mg/mL intravenously* • *2.5 mg/mL subcutaneously*	

LENGTH OF AUTHORIZATION

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)
- Systemic Light Chain Amyloidosis in combination with lenalidomide and dexamethasone: Coverage will be provided for a total of 8 cycles (28-days per cycle).
- Systemic Light Chain Amyloidosis in combination with daratumumab and hyaluronidase-fihj, cyclophosphamide, and dexamethasone: Coverage will be provided for a total of 2 years.
- 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).
- Pediatric Hodgkin Lymphoma: Coverage will be provided for a total of 4 cycles (21-days per cycle).

DOSING LIMITS

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:**
  - 210 billable units every 28 days
  - ~~280 billable units every 28 days~~
- **Multiple Myeloma (initial treatment):**
  - 280 billable units every 42 days for cycles 1-4, then 140 billable units every 42 days cycles 5-9
- Pediatric Hodgkin Lymphoma:
  - 105 billable units every 21 days
- All Other Indications:
  - 140 billable units every 21 days

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the Medical Policy and a health plan, the express terms of the health plan will govern.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

SOURCES

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EFFECTIVE DATE 6/30/2021

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