I. PURPOSE
To define and describe the accepted indications for Velcade (bortezomib) usage in the treatment of cancer

II. DEFINITIONS

**Velcade (bortezomib):** a reversible inhibitor of the 26S proteasome, a protein complex that degrades ubiquitinated proteins. This inhibition affects cancer cells in a number of ways, including altering regulatory proteins, which control cell cycle progression and activation. Inhibition of the proteasome results in cell cycle arrest and apoptosis.

Velcade (bortezomib) is FDA approved for the treatment of members with multiple myeloma and mantle cell lymphoma.

Velcade (bortezomib) is available as 3.5 mg single use vial.

III. POLICY

New Century is responsible for processing all medication requests from network ordering providers. Medications not authorized by New Century may be deemed as not approvable and therefore not reimbursable.

Treatment request outside the approved FDA manufacturer labeling or CMS approved compendia must follow CMS Medicare Benefit Policy Manual Chapter 15. If references are not produced, delays may occur to the processing of such request.

**Inclusion Criteria:** Velcade (bortezomib) may be considered medically necessary when any of the following selection criteria is met:

1. **Multiple Myeloma**
   a. The member has a diagnosis of solitary plasmacytoma, smoldering multiple myeloma, or multiple myeloma **AND**
   b. Velcade (bortezomib) is being used as **ONE** of the following:
      i. Primary chemotherapy
      1. In combination with dexamethasone AND doxorubicin, cyclophosphamide, lenalidomide, or thalidomide for transplant candidates **OR**
2. In VTD-PACE (bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide and etoposide) regimen for transplant candidates.

ii. Relapse/Salvage chemotherapy with the same regimen for disease relapse > 6 months following primary chemotherapy.

iii. Relapse/Salvage chemotherapy for disease relapse or for progressive or refractory disease following primary chemotherapy as ONE of the following:

1. In combination with dexamethasone AND daratumumab, lenalidomide, cyclophosphamide, bendamustine, liposomal doxorubicin, or elotuzumab

2. In combination with dexamethasone

3. In VTD-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide) regimen

4. In combination with panobinostat and dexamethasone for members who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent

5. Combination with pomalidomide and dexamethasone for members who have received at least two prior therapies, including an immunomodulatory agent and a proteasome inhibitor, and have demonstrated disease progression on or within 60 days of completion of the last therapy.

iv. Maintenance therapy as a single agent following response to primary myeloma therapy or in stable disease following stem cell transplant.

2. Non-Hodgkin’s Lymphoma (NHL)

a. The member has a diagnosis of mantle cell lymphoma AND

b. Velcade (bortezomib) is being used as a single agent as second line therapy for relapsed, refractory, or progressive disease or as less aggressive induction therapy with VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone) regimen.

Exclusion Criteria: Velcade (bortezomib) is not considered medically necessary when any of the following selection criteria is met:

1. Velcade (bortezomib) is being used after disease progression with the same regimen.

2. Dosing exceeds single dose limit of Velcade (bortezomib) 1.6 mg/m².

3. Maintenance dosing exceeds 6.4 mg/m² every 35 day cycle or 1.3 mg/m² every 2 weeks.

4. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature may be deemed as not approvable and therefore not reimbursable.
IV. PROCEDURE

Requests for Velcade (bortezomib) shall be reviewed for appropriateness per FDA approved product labeling, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) clinical guidelines, or CMS approved compendia.

1. Dosage and Administration
   a. Multiple myeloma:
      i. Initial therapy in combination with melphalan and prednisone: 1.3 mg/m² IV bolus or subcutaneous injection on days 1, 4, 8, 11, 22, 25, 29, and 32 for Cycles 1-4 followed by a rest for 10 days. For Cycles 5-9, Velcade (bortezomib) is administered weekly on days 1, 8, 22, and 29 followed by a rest. The regimen is a total of nine six week treatment cycles.
      ii. Relapse: 1.3 mg/m²/dose given as IV bolus or subcutaneous injection twice weekly for 2 weeks (i.e. on days 1, 4, 8, and 11) followed by a 10-day rest; each cycle is 21 days. Consecutive doses should be administered at least 72 hours apart. For extended therapy or more than 8 cycles, either a weekly schedule (once a week for 4 weeks on days 1, 8, 15, and 22) every 35 day cycle or 1.3 mg/m² every 2 weeks may be used for maintenance.
   b. Mantle Cell Lymphoma
      i. Relapsed: 1.3 mg/m²/dose given as IV bolus or subcutaneous injection twice weekly for 2 weeks (i.e. on days 1, 4, 8, and 11) followed by a 10-day rest; each cycle is 21 days. Consecutive doses should be administered at least 72 hours apart. For extended therapy or more than 8 cycles, either the standard schedule or a weekly schedule (once a week for 4 weeks on days 1, 8, 15, and 22) followed by a 13 day rest period may be used for maintenance.
   c. Weekly bortezomib dosing: Guidelines for weekly dosing varies in the literature. Dose range include 1.3 mg/m² to 1.6 mg/m² weekly intravenous or subcutaneous administration (please see reference section for further details).

2. Dosage Adjustments
   a. Renal impairment: Dosage adjustments are not required.
   b. Mild hepatic impairment (bilirubin ≤1 times ULN and AST >UNL or bilirubin >1-1.5 times ULN): No initial dose adjustment required.
   c. Moderate (bilirubin >1.5-3 times ULN) to severe hepatic impairment (bilirubin >3 times ULN): Reduce initial dose to 0.7 mg/m² in the first cycle. May consider dose escalation to 1 mg/m² or further dose reduction to 0.5 mg/m² in subsequent cycles based on member tolerance.
   d. Hematologic toxicities: Interrupt and hold Velcade (bortezomib) therapy for grade 4 hematologic toxicities; re-institute once the toxicity has resolved at a 25% reduced dose.
   e. Non-hematologic toxicities- grade 3: Interrupt and hold Velcade (bortezomib) therapy for grade 3 non-hematologic toxicities (excluding neuropathy); re-institute once the toxicity has resolved at a 25% reduced dose.
   f. Central nervous system toxicities: Decrease Velcade (bortezomib) to 1 mg/m² if grade 1 with pain or grade 2 peripheral neuropathy occurs; hold therapy until toxicity resolves and...
re-institute at 0.7 mg/m²/WEEK if grade 2 with pain or grade 3 peripheral neuropathy occurs; discontinue Velcade (bortezomib) therapy if grade 4 peripheral neuropathy occurs.

3. **Monitoring**
   a. **Laboratory Parameters**
      i. Monitor complete blood counts (CBC) frequently and platelet count, (prior to each use) during treatment.
      ii. In members with a high tumor burden prior to treatment, closely monitor for tumor lysis syndrome (e.g., serum electrolytes, serum creatinine, lactate dehydrogenase, uric acid).
      iii. In diabetic member on oral hypoglycemics, monitor blood glucose levels closely
      iv. Monitor serum and urine M-protein (monoclonal immunoglobulin secreted by myeloma cells), plasma cells in bone marrow, and calcium.
   b. **Physical Findings**
      i. Monitor members for symptoms of peripheral neuropathy (e.g., burning sensation, hyperesthesia, hypoesthesias, paresthesia, discomfort, neuropathic pain or weakness).
      ii. In members with pre-existing or risk factors for heart disease, observe for symptoms of cardiac toxicity (e.g., congestive heart failure, cardiogenic shock, pulmonary edema).
      iii. Observe members for signs and symptoms of serious toxicity including dehydration, new or worsening cardiopulmonary symptoms, abnormal bleeding (e.g., GI, intracerebral hemorrhage), and reversible posterior leukoencephalopathy syndrome.
   c. **Drug interactions:** Members who are concomitantly receiving Velcade (bortezomib) and drugs that are inhibitors or inducers of CYP3A4 should be closely monitored for either toxicities or reduced efficacy.

V. **APPROVAL AUTHORITY**
   1. Review – UM Department
   2. Final Approval – UM Committee

VI. **ATTACHMENTS**

VII. **REFERENCES**


