Medicare Advantage Medical Utilization Review Policy

Policy:	**Oncology (Injectable) – Bortezomib Utilization Management Medical Policy** • Velcade® (bortezomib intravenous or subcutaneous injection – Takeda, generic)
Date:	12/11/2023
Applicable Lines of Business:	Medicare Advantage - Medical
Applicable States:	NGS, J6: Wisconsin, Minnesota, Illinois NGS, JK: New York, Connecticut, Massachusetts, Maine, New Hampshire, Rhode Island, Vermont

OVERVIEW

Bortezomib, a proteasome inhibitor, is indicated in adults with the following conditions:[1]

1. **Mantle cell lymphoma**.
2. **Multiple myeloma**.

Guidelines

Bortezomib is mentioned in several guidelines published by the National Comprehensive Cancer Network (NCCN).[2-11]

- **Acute lymphoblastic leukemia:** Guidelines for adults (version 3.2023 – October 9, 2023) and for pediatric patients (version 3.2024 – October 31, 2023) include bortezomib + chemotherapy among the other recommended regimens for relapsed or refractory disease.[3,4]
- **B-cell lymphomas:** Guidelines (version 6.2023 – October 10, 2023) recommend bortezomib (as a component of (VR-CAP [bortezomib/rituximab/cyclophosphamide/ doxorubicin/prednisone]) as a preferred less aggressive therapy option for the initial treatment of patients (induction therapy) with newly diagnosed mantle cell lymphoma.[5] Bortezomib ± rituximab is also listed as second-line and subsequent therapy for relapsed or refractory mantle cell lymphoma. For patients with relapsed or refractory multicentric Castleman's disease, bortezomib ± rituximab is listed among the treatment options.
- **Kaposi sarcoma:** Guidelines (version 1.2024 – November 7, 2023) include bortezomib among the subsequent systemic therapy options for patients who have relapsed or refractory disease.[6]
- **Classic Hodgkin lymphoma:** Guidelines for pediatric disease (version 2.2023 – March 9, 2023) include bortezomib/ifosfamide/vinorelbine among the subsequent therapy options for relapsed or refractory disease.[7]
- **Multiple myeloma:** Bortezomib features prominently in the NCCN Multiple Myeloma clinical practice guidelines (version 2.2024 – November 1, 2023).[8] Bortezomib-containing regimens are listed as preferred for primary therapy (transplant and nontransplant candidates) and previously treated disease. Bortezomib is also a component of multiple other regimens across the spectrum of disease. For maintenance therapy, bortezomib ± lenalidomide capsules (and ± dexamethasone for transplant candidates) are also listed as treatment options.
- **Systemic light chain amyloidosis:** Guidelines (version 1.2024 – October 18, 2023) list bortezomib alone or in combination with other agents for primary therapy (transplant and non-transplant candidates) and previously treated disease.[9] NCCN notes that bortezomib was well tolerated at doses up to 1.6 mg/m^2 on a once-weekly schedule and 1.3 mg/m^2 on a twice-weekly schedule. The once-weekly regimen was associated with lower neurotoxicity.
- **T-cell lymphomas:** Guidelines (version 1.2023 – January 5, 2023) recommend bortezomib (category 2A) as an alternative regimen for second-line or subsequent therapy.[11]
- **Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma:** Guidelines (version 1.2024 – September 28, 2023) recommend bortezomib/dexamethasone/rituximab as a preferred regimen for primary therapy and for previously treated disease.[10]

Dosing Information

Bortezomib must be reconstituted prior to intravenous or subcutaneous administration. Dosing regimens vary and are dependent upon concomitant therapies and tolerability.[1,7,9] Additionally, dose modifications with bortezomib are recommended for the management of hematological toxicity (e.g., neutropenia, thrombocytopenia), non-hematological toxicity (e.g., Grade 3 or higher), peripheral neuropathy, and hepatic impairment. This may include reducing the dose or withholding the drug until the toxicity is resolved. See the Prescribing Information for more detail.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of bortezomib. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. All approvals are provided for the duration noted below.

This policy incorporates Medicare coverage guidance as set forth in National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs), as well as in companion policy articles and other guidance applicable to the relevant service areas. These documents are cited in the References section of this policy. In some cases, this guidance includes specific lists of HCPCS and ICD-10 codes to help inform the coverage determination process. The Articles that include specific lists for billing and coding purposes will be included in the Reference section of this policy. However, to the extent that this policy cites such lists of HCPCS and ICD-10 codes, they should be used for reference purposes only. The presence of a specific HCPCS or ICD-10 code in a chart or companion article to an LCD is not by itself sufficient to approve coverage. Similarly, the absence of such a code does not necessarily mean that the applicable condition or diagnosis is excluded from coverage.

Note: Conditions for coverage outlined in this Medicare Advantage Medical Policy may be less restrictive than those found in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles. Examples of situations where this clinical policy may be less restrictive include, but are not limited to, coverage of additional indications supported by CMS-approved compendia and the exclusion from this policy of additional coverage criteria requirements outlined in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Velcade is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Mantle Cell Lymphoma.

Criteria. Approve for 1 year if the patient meets both of the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following criteria (i or ii):
- **i.** The patient has previously tried at least one other therapy for mantle cell lymphoma; OR
  Note: Examples of other therapies for mantle cell lymphoma include regimens containing a rituximab product, cytarabine, cisplatin, cyclophosphamide, doxorubicin, vincristine, or bendamustine.
- **ii.** The medication is used in combination with at least one other agent.
  Note: Examples of other agents used in combination with Velcade for mantle cell lymphoma include a rituximab product, bendamustine, cyclophosphamide, and doxorubicin.

Dosing. Approve if the requested dosing meets the following (A and B):
A) Each individual dose must not exceed 1.3 mg/m^2 administered intravenously or subcutaneously.
B) The patient receives a maximum of six infusions over a 28-day period.

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2. Multiple Myeloma.

Criteria. Approve for 1 year if the patient meets both of the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following criteria (i or ii):
- **i.** The medication will be used in combination with at least one other agent; OR
  Note: Examples of other agents that may be used in combination with Velcade include dexamethasone, cyclophosphamide, doxorubicin, Doxil® (doxorubicin liposomal injection), Revlimid® (lenalidomide capsules), Thalomid® (thalidomide capsules), cisplatin, etoposide, Darzalex® (daratumumab for injection), Pomalyst (pomalidomide capsules), bendamustine, Empliciti® (elotuzumab for injection), Farydak® (panobinostat capsules).
- **ii.** The medication is being used for maintenance therapy.

Dosing. Approve if dosing meets the following (A and B):
A) Each individual dose must not exceed 1.6 mg/m^2 administered intravenously or subcutaneously.
B) The patient receives a maximum of six infusions over a 28-day period.

OTHER USES WITH SUPPORTIVE EVIDENCE

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3. Acute Lymphoblastic Leukemia.

Criteria. Approve for 1 year if the patient has relapsed or refractory disease.

Dosing. Approve if the requested dosing meets the following (A and B):
A) Each individual dose must not exceed 1.6 mg/m^2 administered intravenously or subcutaneously; AND
B) The patient receives a maximum of six infusions over a 28-day period.

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4. Kaposi Sarcoma.

Criteria. Approve for 1 year if the patient meets the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient has tried at least one systemic chemotherapy.
Note: Examples of systemic chemotherapies include doxorubicin and paclitaxel.

Dosing. Approve if the requested dosing meets the following (A and B):
A) Each individual dose must not exceed 1.6 mg/m^2 administered intravenously or subcutaneously; AND
B) Patient receives a maximum of three infusions over a 28-day period.

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5. Castleman's Disease.

Criteria. Approve for 1 year if the patient meets ALL of the following (A, B and C):
A) Patient is ≥ 18 years of age; AND
B) Patient has multicentric Castleman's disease; AND
C) Patient has relapsed, refractory, or progressive disease.

Dosing. Approve if the requested dosing meets the following (A and B):
A) Each individual dose must not exceed 1.6 mg/m^2 administered intravenously or subcutaneously; AND
B) The patient receives a maximum of six infusions over a 28-day period.

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6. Classic Hodgkin Lymphoma.

Criteria. Approve for 1 year if the patient has tried at least one systemic chemotherapy regimen.
Note: Examples of systemic chemotherapies used in regimens for Hodgkin lymphoma include doxorubicin, bleomycin, vincristine, etoposide, and dacarbazine.

Dosing. Approve if the requested dosing meets the following (A and B):
A) Each individual dose must not exceed 1.6 mg/m^2 administered intravenously or subcutaneously; AND
B) Patient receives a maximum of six infusions over a 28-day period.

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7. Systemic Light Chain Amyloidosis.

Criteria. Approve for 1 year if the patient is ≥ 18 years of age.

Dosing. Approve if the requested dosing meets the following (A and B):
A) Each individual dose must not exceed 1.6 mg/m^2 administered intravenously or subcutaneously.
B) The patient receives a maximum of six infusions over a 28-day period.

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8. T-Cell Lymphoma.

Criteria. Approve for 1 year if the patient meets the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient has tried at least one systemic therapy.
Note: Examples of systemic therapies include EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), Adcetris (brentuximab vedotin) + CHP (cyclophosphamide, doxorubicin, and prednisone), zidovudine + interferon, CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone), HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine.

Dosing. Approve if the requested dosing meets the following (A and B):
A) Each individual dose must not exceed 1.6 mg/m^2 administered intravenously or subcutaneously; AND
B) Patient receives a maximum of six infusions over a 28-day period.

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9. Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma.

Criteria. Approve for 1 year if the patient meets the following (A and B):
A) Patient is ≥ 18 years of age; AND
B) The medication will be used in combination with rituximab and dexamethasone.

Dosing. Approve the following dosing:
A) Each individual dose must not exceed 1.6 mg/m^2 administered intravenously or subcutaneously.
B) The patient receives a maximum of six infusions over a 28-day period.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of bortezomib is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Velcade® subcutaneous injection or intravenous infusion [prescribing information]. Lexington, MA: Takeda; November 2021.
2. The NCCN Drugs and Biologics Compendium. © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 13, 2023. Search term: bortezomib.
3. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 3.2023 – October 09, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on October 29, 2023.
4. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (version 3.2024 – October 31, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 13, 2023..
5. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 6.2023 – October 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed October 29, 2023.
6. The NCCN Kaposi Sarcoma Clinical Practice Guidelines in Oncology (version 2.2024 – November 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 13, 2023.
7. The NCCN Pediatric Hodgkin Lymphoma Clinical Practice Guidelines in Oncology (version 2.2023 – March 9, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on November 13, 2023.
8. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 2.2024 – November 1, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on Novemer 13, 2023.
9. The NCCN Systemic Light Chain Amyloidosis Clinical Practice Guidelines in Oncology (version 1.2024 – October 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed October 29, 2023.
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11. The NCCN T-Cell Lymphomas Clinical Practice Guidelines in Oncology (version 1.2023 – January 5, 2023). © 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed November 13, 2023.
12. Centers for Medicare and Medicaid Services, National Government Services, Inc, Local Coverage Article: Billing and Coding: Bortezomib – Related to LCD L33394 (A52371) [original date 10/01/2015; revision effective date 10/1/2023]. Accessed on December 11, 2023.
13. Centers for Medicare and Medicaid Services, National Government Services, Inc, Local Coverage Determination (LCD): Drugs and Biologicals, Coverage of, for Label and Off-Label Uses (L33394) [original date 10/01/2015; revision effective date 11/1/2022]. Accessed on December 11, 2023.

HISTORY

Type of Revision	Summary of Changes	Date
Policy created	New Medicare Advantage Medical Policy	07/11/2018

Policy revision	Reviewed and revised original policy created 07/11/2018 in accordance with Local Coverage Article A52371 and Oncology - Velcade Utilization Review Policy.	08/28/2019
Policy revision	Completion of 2019 monthly monitoring process in accordance with Local Coverage Determination L33394, Local Coverage Article A52371, and Oncology – Velcade Utilization Review Policy.	12/11/2019
Policy revision	Non-clinical update to policy to add the statement "This policy incorporates Medicare coverage guidance as set forth in National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs), as well as in companion policy articles and other guidance applicable to the relevant service areas. These documents are cited in the References section of this policy. In some cases, this guidance includes specific lists of HCPCS and ICD-10 codes to help inform the coverage determination process. The Articles that include specific lists for billing and coding purposes will be included in the Reference section of this policy. However, to the extent that this policy cites such lists of HCPCS and ICD-10 codes, they should be used for reference purposes only. The presence of a specific HCPCS or ICD-10 code in a chart or companion article to an LCD is not by itself sufficient to approve coverage. Similarly, the absence of such a code does not necessarily mean that the applicable condition or diagnosis is excluded from coverage."	1/30/2020
Policy revision	*Added the following to the Policy Statement "Note: Conditions for coverage outlined in this Medicare Advantage Medical Policy may be less restrictive than those found in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles. Examples of situations where this clinical policy may be less restrictive include, but are not limited to, coverage of additional indications supported by CMS-approved compendia and the exclusion from this policy of additional coverage criteria requirements outlined in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles." *Updated references	08/07/2020
Policy revision	**AIDS (Acquired Immune Deficiency Syndrome)-Related Kaposi Sarcoma:** This condition was added as an Other Use With Supportive Evidence. Criteria were added to align with recommendations in guidelines and require a patient to have tried at least one systemic chemotherapy. **Classic Hodgkin Lymphoma:** This condition was added as an Other Use With Supportive Evidence. Criteria were added to align with recommendations in guidelines and require a patient to have tried at least one systemic chemotherapy regimen.	11/04/2020
Policy revision	The policy was updated to include generics to Velcade approved for intravenous administration. To align with the approved labeling, the dosing section for all indications was updated to notate that subcutaneous dosing applies only to Velcade (brand).	01/29/2021
Policy revision	**Castleman's Disease:** A requirement that the patient has multicentric disease was added. **Waldenstrom's Macroglobulinemia:** A requirement that bortezomib is used in combination with rituximab and dexamethasone was added.	11/15/2022
Policy revision	**Mantle Cell Lymphoma:** An age requirement of ≥ 18 years was added. **Multiple Myeloma:** An age requirement of ≥ 18 years was added.	12/11/2023

	Castleman's Disease: An age requirement of ≥ 18 years was added. **Kaposi Sarcoma:** An age requirement of ≥ 18 years was added. **Systemic Light Chain Amyloidosis:** An age requirement of ≥ 18 years was added. **Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma:** An age requirement of ≥ 18 years was added. **Acute Lymphoblastic Leukemia:** The condition of approval was changed to as listed; previously listed as "Acute Lymphoblastic Lymphoma". **T-Cell Lymphoma:** Added new approval condition and criteria.	