CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL ONCOLOGY

Bortezomib (Velcade®)

Version: 1.1

EFFECTIVE DATE: 1/1/2024

NantHealth® | Eviti®

Please note the following:

Bortezomib (Velcade®)

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Bortezomib (Velcade): Discussion

Bortezomib belongs to a class of medicines called proteasome inhibitors. As a targeted therapy, Bortezomib works by blocking or slowing down the action of proteasomes inside cells. The function of proteasomes is to break down proteins in both healthy and cancerous cells. As the proteasome is unable to digest the additional proteins within cells, a buildup of proteins develops. The buildup of proteins within cells can lead to programmed cell death.[1] Bortezomib is approved by the Food and Drug Administration (FDA) for the treatment of multiple myeloma and mantle cell lymphoma.[2]

The National Comprehensive Cancer Network (NCCN) endorses bortezomib in the following cancer types: acute lymphoblastic leukemia, B-cell lymphomas, Castleman disease, Kaposi sarcoma, multiple myeloma, pediatric acute lymphoblastic leukemia, pediatric Hodgkin lymphoma, primary cutaneous lymphomas, systemic light chain amyloidosis, T-cell lymphomas, and Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma.[3,4,5,6,7,8,9,10,11,12,13]

Bortezomib has following clinically significant adverse reactions: peripheral neuropathy, hypotension, cardiac toxicity, pulmonary toxicity, gastrointestinal toxicity, thrombocytopenia/neutropenia, tumor lysis syndrome, hepatic toxicity, thrombotic microangiopathy and posterior reversible encephalopathy syndrome (PRES).[2]

Bortezomib: Definitions

- **Food and Drug Administration (FDA)** – The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- **National Comprehensive Cancer Network (NCCN) -** An alliance of over 30 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.

- **Posterior Reversible Encephalopathy Syndrome (PRES)** – A neurologic disorder in which a person presents with visual disturbance, seizure, headaches, and altered mentation.[15]
- **Proteasome Inhibitors** - A drug that blocks the action of proteasome which is a protein complex responsible for cellular protein turnover, which is essential for the homeostasis of cells by blocking the proteasome, the breakdown of proteins that promote cell death is prevented, helping to control cell growth.[16]
- **Thrombotic Microangiopathy** – A group of diseases where small blood vessels get damaged, leading to blood clots. These clots form in tiny blood vessels like capillaries and arterioles, using up platelets.[14]

Bortezomib: Policy

Note: Coverage of bortezomib will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation OR when all criteria are met.

Bortezomib will be considered for coverage when the following criteria are met:

Acute Lymphoblastic Leukemia (ALL)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Therapy as a component of bortezomib plus the chemotherapy regimen for one of the following:
   a) Block 1 Reinduction: vincristine, doxorubicin, prednisone, bortezomib, pegaspargase; with IT hydrocortisone (if CNS positive), IT cytarabine, IT methotrexate
   b) Block 2 Reinduction: etoposide, cyclophosphamide, bortezomib, methotrexate, leucovorin; with IT hydrocortisone and IT cytarabine (if CNS positive), IT methotrexate.[3]

Note: The above regimen is used for T-ALL during relapsed/refractory (R/R) therapy.

B-Cell Lymphomas

HIV-Related B-Cell Lymphomas

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. As a component of bortezomib-ICE (ifosfamide, carboplatin, and etoposide) regimen with or without rituximab for relapsed disease for one of the following:
   a) HIV-related diffuse large B-cell lymphoma
   b) HHV8-positive diffuse large B-cell lymphoma, not otherwise specified
   c) Primary effusion lymphoma

Mantle Cell Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Less aggressive induction therapy as a component of VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone) regimen for one of the following:
   a) Initial therapy for stage I-II disease
   b) Additional therapy for partial response, progression, or relapse after initial treatment with involved site radiation therapy alone
   c) Reinduction therapy, in selected cases, for relapse after initial treatment with chemoimmunotherapy
   d) Classical or indolent TP53 wildtype stage II bulky or noncontiguous, III, or IV disease if not suitable for aggressive induction therapy; OR
4. In the absence of a clinical trial and if not suitable for aggressive induction therapy, consider as less aggressive induction therapy for classical or indolent TP53 mutated stage II bulky or noncontiguous, III, or IV disease as a component of VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone) regimen; OR
5. Useful in certain circumstances as second-line and subsequent therapy as a single agent or in combination with rituximab for one of the following:
   a) Stage I-II disease with partial response, progression, or relapse after prior treatment with chemoimmunotherapy
   b) Classical or symptomatic indolent stage II bulky or noncontiguous, III, or IV disease in patients who have stable or progressive disease or a partial response with substantial disease after induction therapy
   c) Relapsed or refractory disease (if not previously given).[4]

Note: TP53 mutation has been associated with poor prognosis in patients treated with conventional therapy, including transplant, clinical trial is strongly recommended.

Castleman Disease

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Used as subsequent therapy with or without rituximab for multicentric CD that has progressed following treatment of relapsed/refractory or progressive disease.[5]

Kaposi Sarcoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Subsequent systemic therapy, given alone (no HIV) or with antiretroviral therapy (ART) for people with HIV, for relapsed/refractory advanced cutaneous, oral, visceral, or nodal disease that has progressed on or not responded to first-line systemic therapy, and progressed on alternate first-line systemic therapy.[6]

Multiple Myeloma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Primary therapy for symptomatic multiple myeloma for one of the following:

a) In combination with dexamethasone, daratumumab and lenalidomide for transplant candidates
b) In combination with daratumumab, melphalan hydrochloride, and prednisone for non-transplant candidates
c) In combination with dexamethasone and doxorubicin for transplant candidates
d) In combination with dexamethasone and thalidomide for transplant candidates
e) In combination with daratumumab, thalidomide, and dexamethasone for transplant candidates
f) As part of VRd-lite (bortezomib, lenalidomide, and dexamethasone) regimen for non-transplant candidates and could be used for frail patients; OR

4. Primary therapy for symptomatic multiple myeloma or for disease relapse after 6 months following primary induction therapy with the same regimen for one of the following:
   a) In combination with dexamethasone and lenalidomide
   b) In combination with dexamethasone and cyclophosphamide for one of the following:
      i. Initial treatment in patients with acute renal insufficiency or those who have no access to bortezomib/lenalidomide/dexamethasone
      ii. Primary therapy
      iii. When used in the relapse setting; OR
   c) In combination with dexamethasone, cyclophosphamide, and daratumumab for one of the following:
      i. Primary therapy, regardless of transplant status
      ii. In the relapse setting; OR
   d) In combination with dexamethasone for non-transplant candidates
   e) VTD-PACE (bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide) regimen for transplant candidates (generally reserved for aggressive multiple myeloma); OR

5. Maintenance therapy for symptomatic multiple myeloma after response to primary myeloma therapy or for response or stable disease following either an autologous hematopoietic cell transplant (HCT) or tandem autologous or allogeneic HCT for high-risk patients for one of the following:
   a) As a single agent
   b) In combination with lenalidomide (dual maintenance recommended for high-risk disease)
   c) In combination with lenalidomide and dexamethasone for transplant candidates (dual maintenance recommended for high-risk disease); OR

6. Therapy for previously treated multiple myeloma for relapse or progressive disease in one of the following:
   a) Combination with dexamethasone and lenalidomide
   b) Combination with dexamethasone and daratumumab if lenalidomide-refractory
   c) Combination with pomalidomide and dexamethasone for patients who have received at least two prior therapies, including an immunomodulatory agent and a proteasome inhibitor, and who have demonstrated disease progression on or within 60 days of completion of the last therapy
   d) Combination with dexamethasone and liposomal doxorubicin
   e) Combination with dexamethasone and cyclophosphamide

f) Combination with dexamethasone, cyclophosphamide, and daratumumab
g) Combination with elotuzumab and dexamethasone
h) Combination with selinexor and dexamethasone (once weekly)
i) Combination with dexamethasone
j) VTD-PACE (bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide) regimen (generally reserved for aggressive multiple myeloma); OR

7. Therapy for previously treated multiple myeloma for late relapse or progressive disease (>3 prior therapies) in combination with bendamustine and dexamethasone; OR

8. Treatment in combination with dexamethasone for the management of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome for one of the following:
   a) Induction therapy for transplant-eligible patients
   b) For transplant-ineligible patients.[7]

Pediatric Acute Lymphoblastic Leukemia

1. Less than or equal to 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Relapsed/refractory Ph-negative B-ALL; OR
4. In combination with dasatinib or imatinib for relapsed/refractory Ph-positive B-ALL as a component of COG AALL07P1 regimen; OR
5. T-LBL (T-lymphoblastic lymphoma) in combination with BFM backbone chemotherapy; OR
6. Relapsed/refractory T-ALL as a component of a bortezomib-containing regimen (e.g. bortezomib, vincristine, doxorubicin, pegaspargase, and prednisone or dexamethasone).[8]

Pediatric Hodgkin Lymphoma

1. Less than or equal to 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Subsequent therapy in combination with ifosfamide and vinorelbine for relapsed or refractory disease.[9]

Primary Cutaneous Lymphomas - Mycosis Fungoides/Sezary Syndrome

1. At least 18 years or older; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Systemic therapy as a single agent subsequent treatment for refractory disease to multiple previous therapies for one of the following:
   a) Stage IIB mycosis fungoides (MF) with limited tumor lesions
   b) Stage IIB MF with generalized tumor lesions
   c) Stage III MF
   d) Stage IVA1 or IVA2 Sezary syndrome
   e) Stage IVA2 non-Sezary or stage IVB visceral disease (solid organ)
   f) Limited cutaneous lesions with large cell transformation (LCT)
   g) Generalized cutaneous or extracutaneous lesions with LCT.[10]

Systemic Light Chain Amyloidosis

1. At least 18 years or older; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Treatment for a newly diagnosed disease or consider for relapsed/refractory disease as a repeat of initial therapy if relapse-free for several years for one of the following:
   a) In combination with daratumumab and hyaluronidase-fihj, cyclophosphamide, and dexamethasone
   b) In combination with cyclophosphamide and dexamethasone
   c) In combination with dexamethasone
   d) In combination with lenalidomide and dexamethasone
   e) If ineligible for hematopoietic cell transplant, may be given in combination with dexamethasone and melphalan, when used as primary therapy; OR
4. Treatment for relapsed/refractory disease for one of the following:
   a) As a single agent
   b) In combination with dexamethasone
   c) In combination with cyclophosphamide and dexamethasone
   d) in combination with dexamethasone and melphalan.[11]

T- Cell Lymphomas

Adult T- Cell Leukemia/Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Second-line or subsequent therapy as a single agent for non-responders to first-line therapy for acute or lymphoma subtypes

Breast Implant-Associated Anaplastic Large Cell Lymphoma (ALCL)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Second line and subsequent therapy for relapsed/refractory disease in patients with no intention to proceed to transplant, as a single agent

Hepatosplenic T- Cell Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Therapy as a single agent for refractory disease after 2 first-line therapy regimens in patients with no intention to proceed to transplant

Peripheral T-Cell Lymphomas

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Single-agent as initial palliative intent therapy or second line and subsequent therapy for relapsed/refractory for one of the following:
   a) Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS)
   b) Enteropathy-associated T-cell lymphoma (EATL)
   c) Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)
   d) Angioimmunoblastic T-cell lymphoma (AITL)
   e) Nodal peripheral T-cell lymphoma with TFH phenotype (PTCL, TFH)
   f) Follicular T-cell lymphoma (FTCL)
   g) Anaplastic large cell lymphoma (ALCL).[12]

Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Used as primary therapy or consider for relapse if previously used as primary therapy that was well tolerated and elicited a prolonged response, or as an alternative therapy for previously treated disease with persistent symptoms following primary therapy or that does not respond to primary therapy or for progressive or relapsed disease in combination with dexamethasone and rituximab.[13]

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Bortezomib: References

1. Velcade – Tekeda Manufacturer website. https://www.velcade.com/about-velcade/. Accessed July 10, 2024.
2. Velcade (Bortezomib) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021602s046lbl.pdf. Accessed July 10, 2024.
3. National Comprehensive Cancer Network Guidelines. Acute Lymphoblastic Leukemia. https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed July 10, 2024.
4. National Comprehensive Cancer Network. B-Cell Lymphomas. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed July 10, 2024.
5. National Comprehensive Cancer Network. Castleman Disease.

https://www.nccn.org/professionals/physician_gls/pdf/castleman.pdf. Accessed July 10, 2024.
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7. National Comprehensive Cancer Network. Multiple Myeloma. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed July 10, 2024.
8. National Comprehensive Cancer Network. Pediatric Acute Lymphoblastic Leukemia. https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf. Accessed July 10, 2024.
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14. Hemolytic Uremic Syndrome – StatPearls [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK556038/. Accessed July 10, 2024.
15. Reversible Encephalopathy Syndrome - StatPearls [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK554492/. Accessed July 10, 2024.
16. Bortezomib - StatPearls [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK519559/. Accessed July 10, 2024.

Bortezomib: Coding (CPT®, ICD 10 and HCPCS) *

*Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment.

CODE	DESCRIPTION
B20, C83.30-C83.39, C83.80-C83.89, C85.80-C85.89	B-Cell Lymphomas - HIV-Related B-Cell Lymphomas
C46.0, C46.1, C46.2, C46.3,	Kaposi Sarcoma

C46.4, C46.50, C46.51, C46.52, C46.7, C46.9	
C81.10-C81.19, C81.20-C81.29, C81.30-C81.39, C81.40-C81.49, C81.70-C81.79, C81.90-C81.99, Z85.71	Pediatric Hodgkin Lymphoma
C83.10-C83.19	B-Cell Lymphomas - Mantle Cell Lymphoma
C83.50-C83.59, C91.00-C91.02	Acute Lymphoblastic Leukemia
C84.00-C84.09, C84.10-C84.19	Primary Cutaneous Lymphomas
C84.40-C84.49, C84.60-C84.69, C84.70-C84.79, C86.2, C86.5	T-Cell Lymphomas
C88.0	Waldenström Macroglobulinemia / Lymphoplasmacytic Lymphoma
C90.00, C90.02, C90.10, C90.12, C90.20, C90.22, C90.30, C90.32, Z85.79	Multiple Myeloma
C91.00, C91.02	Pediatric Acute Lymphoblastic Leukemia
D47.Z2, B10.89	B-Cell Lymphomas - Castleman Disease
E85.3, E85.4, E85.81, E85.89, E85.9	Systemic Light Chain Amyloidosis
J9041	Bortezomib

Bortezomib: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2024
2	Policy Review Dates:	6/16/2023, 7/10/2024
3	Policy Revision Dates:	7/10/2024
4	Department Owner:	Medical Affairs
5	NH Advisory Committee Approval Dates:	8/7/2023, 8/15/2024
6	Revision Changes:	7/10/2024 – Additional new definitions added