POLICY: Oncology – Velcade® (bortezomib injection for intravenous or subcutaneous use – Millennium Pharmaceuticals, Inc.)

DATE REVIEWED: 12/11/2019

OVERVIEW

Velcade is a reversible inhibitor of the 26S proteasome, which is a large protein complex that degrades ubiquitinated proteins.[1] The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins and thereby maintaining homeostasis within cells. Velcade disrupts this normal homeostatic mechanism and can lead to cell death.

Velcade is indicated for the following uses:

1. treatment of patients with multiple myeloma; AND
2. treatment of patients with mantle cell lymphoma.

Dosing Information

Velcade must be reconstituted with 0.9% sodium chloride solution prior to intravenous (IV) or subcutaneous (SC) administration. Dosing regimens vary and are dependent upon concomitant therapies and tolerability.[1,7,9] Additionally, dose modifications with Velcade 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.

Guidelines

Velcade is mentioned in several guidelines published by the National Comprehensive Cancer Network (NCCN).

- Multiple Myeloma: Velcade features prominently in the NCCN Multiple Myeloma clinical practice guidelines (version 2.2020 – October 9, 2019).[3] Various Velcade-containing regimens are listed as Preferred for primary therapy (transplant and nontransplant candidates) and previously treated disease. Velcade is also a component of multiple other regimens across the spectrum of disease. For maintenance therapy, Velacade ± Revlimid (lenalidomide capsules) are also listed as treatment options.
- B-Cell Lymphomas: The NCCN B-Cell Lymphomas clinical practice guidelines (version 6.2019 – November 26, 2019) recommend Velcade (as a component of (VR-CAP [Velcade/Rituxancyclophosphamide/doxorubicin/prednisone]) as a less aggressive therapy option for the initial treatment of patients (induction therapy) with newly diagnosed mantle cell lymphoma.[10] VR-CAP, Velcade/bendamustine/rituximab, and Velcade ± rituximab are also listed as second-line therapies for relapsed or refractory mantle cell lymphoma. For patients with relapsed or refractory Castleman's disease, Velcade ± rituximab is listed among the treatment options.
- Systemic Light Chain Amyloidosis: The NCCN systemic light chain amyloidosis guidelines (version 1.2019 – October 26, 2018) list Velcade alone or in combination with other agents for newly untreated and relapsed disease.[11] NCCN notes that Velcade 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.
- Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma: The NCCN Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma clinical practice guidelines (version 2.2019 – September 14, 2018) recommend the following Velcade-based regimens for primary therapy and for previously treated disease: Velcade ± Rituxan, Velcade/dexamethasone, and Velcade/dexamethasone/Rituxan.[15]

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Velcade. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist).

Because of the of the specialized skills required for evaluation and diagnosis of patients treated with Velcade, as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Velcade to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

1. Multiple Myeloma. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) The patient meets ONE of the following criteria (i or ii):

i. The agent will be used in combination with at least one other agent
Note: Examples of other agents that may be used in combination with Velacade 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); OR

ii. The agent is being used for maintenance therapy; AND

B) Velcade is prescribed by or in consultation with an oncologist or a hematologist.

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; AND

B) The patient receives a maximum of six infusions over a 28-day period.

2. Mantle Cell Lymphoma. Approve for 1 year if the patient meets BOTH of the following (A and B):

A) The 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.
Note: Examples of other therapies for mantle cell lymphoma include regimens containing a rituximab product, cytarabine, cisplatin, cyclophosphamide, doxorubicin, vincristine, or bendamustine; OR

ii. Velcade 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; AND

B) Velcade is prescribed by or in consultation with an oncologist or a hematologist.

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; AND
B) The patient receives a maximum of six infusions over a 28-day period.

Other Uses with Supportive Evidence

3. Acute Lymphoblastic Lymphoma (ALL). Approve for 1 year if the patient meets BOTH of the following (A and B):
A) The patient has relapsed or refractory disease; AND
B) The agent is prescribed by or in consultation with an oncologist.

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.

4. Castleman's Disease. Approve for 1 year if the patient meets BOTH of the following (A and B):
A) The patient has relapsed, refractory, or progressive disease; AND
B) The agent is prescribed by or in consultation with an oncologist.

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.

5. Systemic Light Chain Amyloidosis. Approve for 1 year if Velcade is prescribed by or in consultation with an oncologist or a hematologist.

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.

6. Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma. Approve for 1 year if Velcade is prescribed by or in consultation with an oncologist or a hematologist.

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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Velcade has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances not listed in the Authorization Criteria (FDA-approved indications and Other Uses with Supportive Evidence). Criteria will be updated as new published data are available.

REFERENCES

1. Velcade® injection for subcutaneous or intravenous use [prescribing information]. Cambridge, MA: Millennium Pharmaceuticals, Inc.; April 2019.
2. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 27, 2019. Search term: bortezomib.
3. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (Version 2.2020 – October 9, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on November 27, 2019.
4. Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomized, open-label, phase 3 trial. *Lancet.* 2017;389:519-527.
5. Niesvizky R, Flinn IW, Rifkin R, et al. Community-based Phase IIIB trial of three UPFRONT bortezomib-based myeloma regimens. *J Clin Oncol.* 2015;33:3921-3929.
6. Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. *Blood.* 2012;119:4375-4382.
7. Goy A, Bernstein SH, Kahl BS, et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. *Ann Oncol.* 2009;20:520-525.
8. Friedberg JW, Vose JM, Kelly JL, et al. The combination of bendamustine, bortezomib, and rituximab for patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma. *Blood.* 2011;117:2807-2812.
9. Lamm W, Kaufmann H, Raderer M, et al. Bortezomib combined with rituximab and dexamethasone is an active regimen for patients with relapsed and chemotherapy-refractory mantle cell lymphoma. *Haematologica*. 2011;96:1008-1014.
10. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 5.2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed October 16, 2018.
11. The NCCN Systemic Light Chain Amyloidosis Clinical Practice Guidelines in Oncology (Version 1.2019 – October 26, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 27, 2019.
12. Kastritis E, Roussou M, Gavriatopoulou M, et al. Long-term outcomes of primary systemic light chain (AL) amyloidosis in patients treated upfront with bortezomib or lenalidomide and the importance of risk adapted strategies. *Am J Hematol.* 2015;90:E60-E65.
13. Palladini G, Sachchithanantham S, Milani P, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. *Blood.* 2015;126:612-615.
14. Reece DE, Hegenbart U, Sanchorawala V, et al. Long-term follow-up from a phase 1/2 study of single-agent bortezomib in relapsed systemic AL amyloidosis. *Blood.* 2014;124:2498-2506.
15. The NCCN Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma Clinical Practice Guidelines in Oncology (Version 2.2018 – September 14, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 27, 2019.
16. Leblebjian H, Noonan K, Paba-Prada C, et al. Cyclophosphamide, bortezomib, and dexamethasone combination in Waldenstrom macroglobulinemia. Correspondence. *Am J Hematol.* 2015;90:E122.
17. Ghobrial IM, Xie W, Padmanabhan S, et al. Phase II trial of weekly bortezomib in combination with rituximab in untreated patients with Waldenstrom macroglobulinemia. *Am J Hematol.* 2010;85:670-674.
18. Dimopoulos MA, Garcia-Sanz R, Gavriatopoulou M, et al. Primary therapy of Waldenstrom macroglobulinemia (WM) with weekly bortezomib, low-dose dexamethasone, and rituximab (BDR): long-term results of a phase 2 study of the European Myeloma Network (EMN). *Blood.* 2013;122:3276-3282.
19. Ghobrial IM, Hong F, Padmanabhan S, et al. Phase II trial of weekly bortezomib in combination with rituximab in relapsed or relapsed and refractory Waldenstrom macroglobulinemia. *J Clin Oncol.* 2010;28:1422-1428.
20. Gertz MA. Waldenstrom macroglobulinemia: 2017 update on diagnosis, risk stratification, and management. *Am J Hematol.* 2017;92:209-217.
21. The NCCN Pediatric Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 2.2020 – November 25, 2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on December 5, 2019.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New policy	New criteria	03/08/2017
Annual revision	**Multiple Myeloma:** Deleted separate criteria for "in combination with Doxil" (Bii) and added Doxil to the list of examples in next criteria where Velcade is given in combination with dexamethasone. Cisplatin and etoposide were also added as example agents that can be given in combination with dexamethasone. In the dosing section for extended approval and Duration of Therapy in Multiple Myeloma, deleted "if the patient does not have disease progression."	04/04/2018
Early annual revision	**Multiple Myeloma** • Change approval duration to 1 year and clarify that extended approvals are allowed, if the criteria and dosing continue to be met. • For criteria that require Velcade to be taken with another agent, remove the requirement that dexamethasone is part of the treatment regimen. Criteria now more generally require another agent be taken in combination with Velcade and have dexamethasone among the examples of agents that may be taken concomitantly with Velcade. • Criteria for maintenance therapy were changed to apply to all patients taking Velcade as monotherapy for multiple myeloma (previously only applied after stem cell transplantation or after Velcade-based primary therapy). • Update dosing section to note that the maximum dose is 1.6 mg mg/m^2 with a maximum of six doses approved per 28-day treatment cycle (previously criteria listed specific dosing regimens). **Mantle Cell Lymphoma** • Change approval duration to 1 year and clarify that extended approvals are allowed, if the criteria for coverage and dosing continue to be met. • Clarify that criteria for taking Velcade as monotherapy apply in the second-line setting. • Update dosing section to note that the maximum dose is 1.3 mg mg/m^2 with a maximum of 6 doses approved per 28-day treatment cycle (previously criteria listed specific dosing regimens). **Systemic Light Chain Amyloidosis** • Change approval duration to 1 year and clarify that extended approvals are allowed, if the criteria for coverage and dosing continue to be met. • Remove criteria that approve if taken as monotherapy or in combination with dexamethasone ± one other agent. • Update dosing section to note that the maximum dose is 1.6 mg mg/m^2 with a maximum of six doses approved per 28-day treatment cycle (previously criteria listed specific dosing regimens). **Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma** • Change approval duration to 1 year and clarify that extended approvals are allowed, if the criteria for coverage and dosing continue to be met. • Remove criteria that approve if taken as monotherapy or in combination with Rituxan ± dexamethasone. • Update dosing section to note that the maximum dose is 1.6 mg mg/m^2 with a maximum of six doses approved per 28-day treatment cycle (previously criteria listed specific dosing regimens). **Patient has been started on Velcade** • Remove this criterion and address in the criteria section for each approval condition. For each approvable condition, clarify that extended approvals are allowed if the conditions for coverage and dosing continue to be met.	11/14/2018
Annual revision	**Multiple Myeloma:** For the criterion that addresses use as maintenance therapy, remove the requirement that Velcade be given in combination with another agent. **Acute Lymphoblastic Leukemia:** Add this as an approvable off-label indication, if used for relapsed or refractory disease and prescribed by or in consultation with an oncologist. Approvable dosing is similar to the product labeling. **Castleman's Disease:** Add this as an approvable off-label indication, if used for relapsed, refractory, or progressive disease and prescribed by or in consultation with an oncologist. Approvable dosing is similar to the product labeling.	12/11/2019

	Other Cancer Indications: This criterion was deleted from the policy. Indication-specific criteria were added to the policy for these conditions. **Conditions Not Recommended for Coverage:** The recommendation to not cover for Other Indications (Non-Oncology) was changed to apply to all other indications.	