MEDICAL MUTUAL®

Drug Policy

Policy:	**201715-CC**	**Initial Effective Date: 04/17/2017**
Code(s):	**HCPCS J9041, J9044**	**Annual Review Date: 12/20/2018**
SUBJECT:	**Velcade® (bortezomib injection for intravenous or subcutaneous use)**	**Last Revised Date: 12/28/2018**

Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.

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.

Velcade is available as a single-use vial containing 3.5 mg of bortezomib as a sterile lyophilized white to off-white powder. The powder must be reconstituted with 0.9% sodium chloride solution prior to intravenous (IV) or subcutaneous (SC) administration.

GUIDELINES

Multiple Myeloma

Velcade features prominently in the NCCN Multiple Myeloma clinical practice guidelines (version 1.2019).[3] Velcade/dexamethasone/Revlimid® (lenalidomide capsules) and Velcade/dexamethasone/cyclophosphamide are among the Preferred regimens for primary treatment of transplant and non-transplant candidates. Maintenance therapy with Velcade is also a treatment option for non-transplant candidates. For previously treated disease, Velcade/Revlimid/dexamethasone and Velcade/Darzalex (daratumumab IV infusion)/dexamethasone are among the Preferred options. The guidelines note that SC administration of Velcade is the preferred route of administration. In addition to the Preferred regimens, Velcade is recommended in multiple other regimens for multiple myeloma.

Depending on patient characteristics, other treatment alternatives in the first-line setting include Velcade/dexamethasone, Velcade/doxorubacin/dexamethasone, Velcade/Thalomid® (thalidomide capsules)/dexamethasone, and VTD-PACE (Velcade/ dexamethasone/ Thalomid/ cisplatin/ doxorubicin/ cyclophosphamide/ etoposide). Other regimens recommended in certain circumstances for previously treated multiple myeloma include: Velcade/liposomal doxorubicin/dexamethasone, Velcade/cyclophosphamide/dexamethasone, Velcade/dexamethasone,

Velcade/Empliciti/dexamethasone, Velcade/Pomalyst/dexamethasone, Velcade/Farydak/dexamethasone, and VTD-PACE.

B-Cell Lymphomas – Mantle Cell Lymphoma

The NCCN B-Cell Lymphomas clinical practice guidelines (version 5.2018) 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, and Velcade ± Rituxan are also listed as second-line therapies for relapsed or refractory mantle cell lymphoma.

Systemic Light Chain Amyloidosis

The NCCN systemic light chain amyloidosis guidelines (version 1.2019) 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) 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 an Express Scripts 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.**[1-3] 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.** Velcade will be used in combination with at least one other agent (e.g., 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. Velcade is used as a single-agent 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.

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

Dosing regimen varies and is dependent upon concomitant therapies and tolerability. Individual doses up to 1.6 mg/m^2 have been evaluated in the literature.[1,4-6] Refer to the Appendix for more specific dosing regimens recommended in the prescribing information. Note: 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.

Duration of Therapy. Extended approvals are allowed if the patient continues to meet the criteria and dosing (see above).

- Therapy is individualized with careful consideration of the risks and benefits of retreatment or continued treatment. Extended therapy may be administered.

NOTE TO NURSE CLINICIAN: Approval duration should align with dose management criteria (for example, if 8 cycles are approved, the approval duration should be aligned with the duration necessary to complete 8 cycles; if 12 cycles are requested, the approval should be for 1 year).

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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 (e.g., regimens containing one or more of the following agents: rituximab [Rituxan], cytarabine, cisplatin, cyclophosphamide, doxorubicin, vincristine, or bendamustine); OR

ii. Velcade is used in combination with at least one other agent (e.g., Rituxan® [rituximab injection], bendamustine, cyclophosphamide, doxorubicin, prednisone); 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.

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

Dosing regimen varies and is dependent upon concomitant therapies and tolerability.[1,7,9] Refer to the Appendix for more specific dosing regimens recommended in the prescribing information. Note: 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.

Duration of Therapy. Extended approvals are allowed if the patient continues to meet the conditions for coverage and dosing for mantle cell lymphoma (see above).

- Therapy is individualized with careful consideration of the risks and benefits of retreatment or continued treatment. A course of treatment often consists of 8 cycles. Extended treatment with more than 8 cycles may be administered.

NOTE TO NURSE CLINICIAN: Approval duration should align with dose management criteria (for example, if 8 cycles are approved, the approval duration should be aligned with the duration necessary to complete 8 cycles; if 12 cycles are requested, the approval should be for 1 year).

Other Uses with Supportive Evidence

3. 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.

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

In systemic light chain amyloidosis, individual doses up to 1.6 mg/m^2 have been evaluated in the literature.[12-14] Refer to the Appendix for more specific dosing as documented in the prescribing information for approved indications. Note: 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.

Duration of Therapy. Extended approvals are allowed if the patient continues to meet the conditions for coverage and dosing for systemic light chain amyloidosis (see above).

- Data are insufficient to identify optimal treatment. Therapy is individualized with careful consideration of the risks and benefits of retreatment or continued treatment.

NOTE TO NURSE CLINICIAN: Approval duration should align with dose management criteria (for example, if 8 cycles are approved, the approval duration should be aligned with the duration necessary to complete 8 cycles; if 12 cycles are requested, the approval should be for 1 year).

4. **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 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.

   Data are limited. Individual Velcade doses up to 1.6 mg/m^2 have been evaluated in the literature.[2,15] Refer to the Appendix for more specific dosing as documented in the prescribing information for approved indications. Note: 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.

   Duration of Therapy. Extended approvals are allowed if the patient continues to meet the criteria and dosing (see above).
   - In patients who respond to therapy, patients may be followed with observation. Treatment decisions are individualized with careful consideration of the risks and benefit of the selected regimen.

   NOTE TO NURSE CLINICIAN: Approval duration should align with dose management criteria (for example, if 8 cycles are approved, the approval duration should be aligned with the duration necessary to complete 8 cycles; if 12 cycles are requested, the approval should be for 1 year).

5. **Other Cancer Indications.** Forward to the Medical Director for review on a case-by-case basis. Other indications supported in the *NCCN Compendium* include: Castleman's disease (category 2A), adult T-cell leukemia/lymphoma (category 2A), peripheral T-cell lymphoma (category 2B), primary cutaneous CD30+ T-cell lymphoproliferative disorders (category 2A), and mycosis fungoides/sezary syndrome (category 3).[2]

CONDITIONS NOT RECOMMENDED FOR APPROVAL

1. **Other Indications (Non-Cancer).** 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.

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

REFERENCES

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FOR MEDICAL BENEFIT COVERAGE REQUESTS:

Prior approval is required for HCPCS Codes J9041, J9044

HCPCS Code(s):	
J9041	Injection, Bortezomib, 0.1 mg
J9044	Injection, bortezomib, not otherwise specified, 0.1 mg

APPENDIX

Table 1. Previously Untreated Multiple Myeloma (+ Melphalan/Prednisone).^*[^]

	Cycles 1 through 4							
	Day 1	**Day 4**	**Day 8**	**Day 11**	**Day 22**	**Day 25**	**Day 29**	**Day 32**
Velcade	1.3 mg/m^2	1.3 mg/m^2	1.3 mg/m^2	1.3 mg/m^2	1.3 mg/m^2	1.3 mg/m^2	1.3 mg/m^2	1.3 mg/m^2
	Cycles 5 through 9[#]							
Velcade	1.3 mg/m^2	--	1.3 mg/m^2	--	1.3 mg/m^2	--	1.3 mg/m^2	--

[^] Per the product labeling; [*] Refer to the Velcade prescribing information for recommended dose modifications based on toxicity and for dosing schedule for concomitant therapies; [#] For extended therapy of more than 8 cycles, Velcade may be administered on the standard schedule. For relapsed disease, Velcade may be administered on a maintenance schedule once weekly for 4 weeks followed by a 13-day rest period.

Table 2. Previously Untreated Mantle Cell Lymphoma (+ VcR-CAP).^*[^]

	Cycles 1 through 6[^]				
	Day 1	**Day 4**	**Day 8**	**Day 11**	**Days 12-21**
Velcade	1.3 mg/m^2	1.3 mg/m^2	1.3 mg/m^2	1.3 mg/m^2	--

VcR-CAP – Intravenous rituximab, cyclophosphamide, doxorubicin, and oral prednisone; [^] Per the product labeling; [*] Refer to the Velcade prescribing information for recommended dose modifications based on toxicity and for dosing schedule for concomitant therapies; ^ Administered for six 3-week cycles (may continue for two more cycles for a total of eight cycles if response is first seen at cycle 6).

Table 3. Relapsed Multiple Myeloma and Relapsed Mantle Cell Myeloma.[^*]

	Day 1	Day 4	Day 8	Day 11	Days 12-21
Velcade	1.3 mg/m^{2}[#]	1.3 mg/m^{2}	1.3 mg/m^{2}	1.3 mg/m^{2}	--

[^] Per the product labeling; [*] For extended therapy > eight cycles, Velcade may be administered at the standard dose, or, for relapsed multiple myeloma, on a maintenance schedule of once weekly for 4 weeks followed by a 13-day rest period; [#] Patients with multiple myeloma who have previously responded to Velcade (alone or in combination) and who relapse at least 6 months after prior therapy may restart at last tolerated dose.