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Medication Policy Manual | **Policy No:** dru190

Topic: Velcade®, bortezomib | **Date of Origin:** January 1, 2010

Committee Approval Date: November 10, 2017 | **Next Review Date:** October 2018

Effective Date: December 1, 2017

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Bortezomib (Velcade) is chemotherapy medication used to treat multiple myeloma and certain other cancers. It is given via intravenous injection.

Policy/Criteria

I. Most contracts require prior authorization approval of bortezomib prior to coverage. Bortezomib may be considered medically necessary when criterion A, B, C, or D below is met:

A. A diagnosis of multiple myeloma.

OR

B. A diagnosis of mantle cell lymphoma.

OR

C. A diagnosis of Waldenström's macroglobulinemia.

OR

D. A diagnosis of systemic light chain amyloidosis

II. Administration and Authorization Period

A. Regence Pharmacy Services does not consider bortezomib to be a self-administered medication.

B. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Bortezomib is considered investigational when used for all other conditions, including but not limited to:

A. Colorectal cancer

B. Cutaneous T-cell lymphoma (CTCL) (e.g. Mycosis fungoides, Sezary syndrome)

C. Malignant melanoma

D. Non-cutaneous peripheral T-cell lymphoma (PTCL)

E. Non-small cell lung cancer

F. Other lymphomas (not otherwise listed)

G. Prostate cancer

H. Renal cell carcinoma

Position Statement

Summary

- Bortezomib is an intravenously or subcutaneously administered chemotherapy agent that has been found to be safe and effective when used in the treatment of multiple myeloma, mantle cell lymphoma, an aggressive type of non-Hodgkin's (B-cell) lymphoma, and Waldenström's macroglobulinemia.
- Bortezomib is currently being studied in several other types of cancer; however, evidence is preliminary and larger studies are needed to establish safety and efficacy in these conditions.

Clinical efficacy

MULTIPLE MYELOMA

- Several large, randomized controlled trials have evaluated the efficacy of bortezomib in the treatment of multiple myeloma (MM). [1-5]
    * These trials used bortezomib in various combination regimens, including use with high-dose dexamethasone (Vd), liposomal doxorubicin, melphalan + prednisone (VMP), VMP + thalidomide (VMP-VT), and with lenalidomide +dexamethasone (RVD). Regimens varied, depending on the prior therapies and eligibility for a hematopoietic stem cell transplant (HSCT).
    * Response rates were similar across all of the trials which helps to support the potential benefit of bortezomib in MM.
- The National Comprehensive Cancer Network (NCCN) Multiple Myeloma treatment guideline lists bortezomib as one of several potential options for primary induction therapy as well as for salvage therapy for MM and light chain amyloidosis, a related plasma cell disorder. Bortezomib is also listed as a maintenance therapy when used after stem cell transplant. [6]

MANTLE CELL LYMPHOMA

- A large, open-label, phase 3 study compared VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone) versus R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) in 487 subjects with newly diagnosed mantle cell lymphoma who were ineligible or not considered for stem-cell transplantation therapy. [7]
    * After a median follow-up of 40 months, median progression-free survival was 14.4 months in the R-CHOP group versus 24.7 months in the VR-CAP group (hazard ratio favoring the VR-CAP group, 0.63; P<0.001).
    * The rate of 4-year overall survival rate was higher in the VR-CAP group compared to RCHOP (64% vs. 54%, respectively).
- Additionally, several uncontrolled trials (numbers ranging from 26 to 155 subjects) have evaluated the use of bortezomib in the treatment of relapsed or refractory mantle cell lymphoma. [8-11] Evidence from these trials is lower quality as there was no blinding or comparator group.
- Despite the limitations, the quality of the evidence for bortezomib is typical of that which is available for other medications used in the treatment of relapsed or refractory mantle cell lymphoma. The fact that all of the trials reported similar tumor response rates helps to support the potential benefit of bortezomib in this population.

WALDENSTRÖM'S MACROGLOBULINEMIA

- Waldenström macroglobulinemia (WM) is a rare condition (approximately three per million per year) affecting the bone marrow and blood. The median age of diagnosis is 64 years of age. Treatment is indicated only in patients with symptomatic WM.

- Patients with asymptomatic (smoldering) WM typically do not require treatment because they have overall survival rates approximating that of the normal population.
- Bortezomib has been studied alone and in combination with rituximab in the treatment of relapsed or refractory WM. Although the studies are of low quality and only measure biochemical response, there are few options available for the treatment of patients with this condition. [5,12,13]
- NCCN treatment guidelines for Waldenström's Macroglobulinemia recommend bortezomib with or without rituximab as one of many treatment regimens for primary treatment and salvage treatment of WM (Category 2A). [14]

SYSTEMIC LIGHT CHAIN AMYLOIDOSIS (AL)

- Systemic light chain amyloidosis is a relatively rare plasma cell disorder, characterized by a low number of abnormal monoclonal plasma cells, relative to multiple myeloma. However, the plasma cells produce protein, which deposits in visceral tissues (such as the kidney, heart, liver, and spleen) and can lead to end organ dysfunction. Therefore, it is recommended that patients with evidence of organ involvement (deposition of amyloid in tissues) be treated, targeting the underlying plasma cell disorder. [15]
- Two prospective Phase 2 trials evaluated bortezomib for AL:
  * A prospective phase 2 study in 31 patients with relapsed primary systemic amyloidosis reported high response rates with bortezomib (Velcade). [16]
  * Another prospective, Phase 2 trial evaluated bortezomib + dexamethasone induction therapy followed by conditioning with bortezomib and high-dose melphalan (HDM) and autologous stem cell transplantation. Most patients (77%) had a complete or very good partial hematologic response. There was no difference in overall survival at 36 months.
  * Both trials lacked a comparator group and had a small sample size.
- Despite the limitations of the trials, the quality of the evidence for bortezomib is typical of that which is available for other medications used in the treatment of AL. The fact that both of the trials reported similar response rates helps to support the potential benefit of bortezomib in this population.
- NCCN treatment guidelines list bortezomib in combination with dexamethasone with or without cyclophosphamide or melphalan is one of many potential treatment regimens for AL. [15]

OTHER CANCERS

- Bortezomib did not demonstrate any clinical benefit in patients with metastatic colorectal cancer, non-small cell lung cancer, B-cell chronic lymphocytic leukemia, renal cell carcinoma, metastatic malignant melanoma, metastatic prostate cancer, or T-cell leukemia/lymphoma in small, preliminary trials. [15,17-24]

- A small case series evaluated 15 patients who received single agent bortezomib for cutaneous T-cell lymphomas (CTCL) or peripheral T-cell lymphoma (PTCL). All patients had received prior treatment(s). Two of the patients with PTCL, and ten patients with mycosis fungoides (MF), a type of CTCL, were evaluated for efficacy. [25] Additional studies of better design are necessary to establish the safety and effectiveness in these patient populations. Although the NCCN non-Hodgkin's lymphoma (NHL) treatment guideline lists bortezomib as a potential treatment option for T-cell lymphomas, its use in these conditions is considered investigational because the evidence is of such poor quality and there are many other options. Of note, the NCCN recommendation is Category 3 for MF, indicating major disagreement among experts that it is an effective therapy. [26]
- Several small Phase 2 studies have explored the use of bortezomib in a variety of other non-Hodgkin's lymphomas [diffuse large B-cell lymphoma (DLBCL), small lymphocytic lymphomas, low grade follicular lymphoma, and marginal zone lymphoma]. The studies are of poor quality as they are small and many are not controlled (no comparator group). Well-designed studies are necessary to establish efficacy and benefit in these populations. [27-31]

Regence Pharmacy Services performs independent analyses of oncology medications. The Regence Pharmacy Services analysis and coverage policy may differ from NCCN guidelines.

Safety [19]

- Peripheral neuropathy is commonly reported with bortezomib (incidence of up to 47%). It is also the most common adverse effect that led to discontinuation of bortezomib during clinical trials.
  * It may be managed by reducing the bortezomib dose or by discontinuing therapy.
  * It is not reversible in all patients.
- Other potentially serious adverse effects with bortezomib include hypotension, cardiac disorders (heart failure, QT prolongation), pulmonary disorders (pneumonitis, Acute Respiratory Distress Syndrome), thrombocytopenia, neutropenia, and acute liver failure.
- Gastrointestinal adverse are common with bortezomib and include nausea, vomiting, diarrhea, constipation and abdominal pain.
- Reactivation of herpes zoster infection was reported in approximately 13% of patients receiving bortezomib (versus 4 to 5% of control group) during one of the multiple myeloma trials. Antiviral prophylaxis should be considered.
- Potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) increase exposure to bortezomib and may, therefore, increase the risk of adverse events.

Dosing and Administration [19]

- Bortezomib is injected intravenously as a 3 to 5 second bolus.
- The dose of bortezomib is based on body surface area. The typical starting dose is 1.3mg/m^2. The frequency of dosing is based on the condition being treated.
- Dose modification or delay of bortezomib therapy is recommended for thrombocytopenia, neutropenia, peripheral neuropathy, and severe (grade 3 or 4) non-hematological toxicities.

Cross References
Afinitor®, everolimus, Medication Policy Manual, Policy No. 178
Darzalex®, daratumumab, Medication Policy Manual, Policy No. 452
Empliciti®, elotuzumab, Medication Policy Manual, Policy No. 453
Farydak®, panobinostat, Medication Policy Manual, Policy No. 397
Kyprolis™, carfilzomib, Medication Policy Manual, Policy No. 282
Ninlaro®, ixazomib, Medication Policy Manual, Policy No. 455
Pomalyst®, pomalidomide, Medication Policy Manual, Policy No. 293
Revlimid®, lenalidomide, Medication Policy Manual, Policy No. 127
Rituxan®, rituximab, Medication Policy Manual, Policy No. 214

Codes	**Number**	**Description**
HCPCS	J9041	Injection, bortezomib, 0.1 mg
ICD-10	C90.00, C90.01, C90.02, C90.10, C90.12, C90.20, C90.22, C90.30, C90.31, C90.32, Z85.79	Multiple Myeloma
ICD-10	C83.10-C83.19, Z85.72	Mantle Cell Lymphoma
ICD-10	E85.9	Systemic Light Chain Amyloidosis
ICD-10	C83.00-C83.09, C88.0, Z85.72, Z85.79	Waldenström's macroglobulinemia

References

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Revision History

Revision Date	Revision Summary
11/10/2017	No changes to coverage criteria with this annual update
7/15/2016	No criteria changes with this update.
6/10/2016	- Add coverage criteria for systemic light chain amyloidosis - Remove the combination of Velcade/Revlimid from "Not Medically Necessary"