

Medication Policy Manual

Policy No: dru190

Topic: Velcade[®], bortezomib

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IMPORTANT REMINDER

This Medical 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 medical policy is to provide a guide to coverage. Medical 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 mantle cell lymphoma.

Policy/Criteria

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

A. A diagnosis of multiple myeloma.

OR

B. A diagnosis of mantle cell lymphoma in patients who have received at least one prior therapy.

II. Administration and Authorization Period

A. Regence 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 not medically necessary when used in combination with lenalidomide (Revlimid[®]).

IV. 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. Metastatic prostate cancer

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

E. Non-small cell lung cancer

F. Renal cell carcinoma

G. Systemic light chain amyloidosis

H. Waldenström's macroglobulinemia

Position Statement

Summary

- Bortezomib is a chemotherapy agent used in the treatment of multiple myeloma and mantle cell lymphoma, an aggressive type of non-Hodgkin's (B-cell) lymphoma. ^[1-3]
- 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.
- The combination of bortezomib and lenalidomide has not been proven to be as safe as or more effective than either medication given alone. The clinical benefit of this combination has not been established.

Clinical efficacy

MULTIPLE MYELOMA

- Several large, randomized controlled trials have evaluated the efficacy of bortezomib in the treatment of multiple myeloma (MM). ^[4-6] Evidence from these trials is unreliable for reasons that include lack of blinding, lack of intent-to-treat analysis and high rates of discontinuation. However, the trials studied a good number of subjects and response rates were similar across all of the trials which helps to support the potential benefit of bortezomib in MM.
 - * A large, open-label, phase III study compared high-dose dexamethasone with bortezomib in 669 subjects with MM whose disease had progressed after response to one to three prior therapies. ^[4]
 - The median time-to-progression for the bortezomib and HD-dexamethasone groups was 6.2 months and 3.5 months, respectively ($p < 0.001$).
 - The overall response rate (complete plus partial response rate) in the bortezomib and HD-dexamethasone treatment groups was 38% and 18%, respectively ($p < 0.001$).

- * A large, open-label, phase III study compared bortezomib with bortezomib plus liposomal doxorubicin in 646 subjects with MM who were refractory to initial treatment or had progressive disease after response to one or more prior therapies. ^[5]
 - The median time-to-progression for the bortezomib and bortezomib plus liposomal doxorubicin groups was 6.5 months and 9.3 months, respectively. The risk of developing disease progression was reduced by 45% with bortezomib plus liposomal doxorubicin (HR = 1.82; 95% CI: 1.41 – 2.35; p = 0.000004).
 - The overall response rates (complete plus partial response rate) for bortezomib and bortezomib plus liposomal doxorubicin were similar (41% and 44%, respectively).

- * A phase III, randomized controlled trial compared melphalan + prednisone with melphalan + prednisone + bortezomib in 682 subjects with newly diagnosed MM who were not candidates for high-dose therapy plus stem cell transplantation. ^[6]
 - The median time to progression was 24.0 months in the bortezomib group and 16.6 months in the melphalan + prednisone group. The hazard ratio in the bortezomib group was 0.48 (p < 0.001).
 - The overall response rates (complete plus partial response rate) were 71% and 35% in the bortezomib and control groups, respectively (p < 0.001).

- 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. ^[3]

- There is recent interest in adding lenalidomide to a combination of bortezomib and dexamethasone for induction prior to bone marrow transplant. Preliminary response rates from an ongoing, uncontrolled study in patients with relapsed/refractory multiple myeloma appear promising. ^[7] A larger, controlled, phase III ECOG study comparing bortezomib/dexamethasone with bortezomib/lenalidomide/dexamethasone is in progress to evaluate the safety and effectiveness of this combination. ^[8]

MANTLE CELL LYMPHOMA

- Several uncontrolled trials (numbers ranging from 30 to 155 subjects) have evaluated the use of bortezomib in the treatment of mantle cell lymphoma. ^[9-11] Evidence from these trials is unreliable as there was no blinding or comparator group.
- Although unreliable, the quality of the evidence for bortezomib is typical of that which is available for other medications used in the treatment of 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.
- National Comprehensive Cancer Network treatment guidelines list bortezomib as a possible 2nd-line option in the treatment of mantle cell lymphoma. ^[2] (See *Appendix A* for recommended first-line options).

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 or metastatic prostate cancer in small, preliminary trials. ^[12-17]
- A small, preliminary, single-arm (uncontrolled) trial studied bortezomib in 27 patients with Waldenström's macroglobulinemia. Total response rates of 26% were reported. Additional studies are necessary to establish the safety and effectiveness in this population. ^[18]
- A small, preliminary, single-arm (uncontrolled) trial studied bortezomib in 18 patients with systemic light chain amyloidosis. Hematologic response occurred in 94% of evaluable patients and 28% of patients had a response in at least one affected organ. ^[19] Additional studies are necessary to establish the safety and effectiveness in this population. National Comprehensive Cancer Network guidelines state that "there are insufficient data to indicate optimal treatment of amyloidosis" and recommend treating patients with amyloidosis in the context of a clinical trial when possible. ^[3]
- 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. ^[20] Additional studies of better design are necessary to establish the safety and effectiveness in these patient populations.

Safety

- 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. ^[1]
 - * 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. ^[1]
- Gastrointestinal adverse are common with bortezomib and include nausea, vomiting, diarrhea, constipation and abdominal pain. ^[1]
- 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. ^[1]
- Potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) increase exposure to bortezomib and may, therefore, increase the risk of adverse events. ^[1]

Dosing and Administration

- 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/m². The frequency of dosing is based on the condition being treated. ^[1]
- Dose modification or delay of bortezomib therapy is recommended for thrombocytopenia, neutropenia, peripheral neuropathy, and severe (grade 3 or 4) non-hematological toxicities. ^[1]

Appendix A: NCCN first-line options for the treatment of mantle cell lymphoma ^[2]

- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab (Rituxan)
- R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with rituximab plus high-dose methotrexate and cytarabine)
- Rituximab + EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
- Modified HyperCVAD with rituximab (Rituxan) maintenance
- NORDIC (rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone alternating with rituximab + high-dose cytarabine)
- Cladribine + rituximab (Rituxan)

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Cross References
Revlimid [®] , lenalidomide, dru 127

Codes	Number	Description
HCPCS	J9041	Injection, bortezomib, 0.1 mg