Reference number(s)
4479-A

STANDARD MEDICARE PART B MANAGEMENT

VELCADE (bortezomib)
bortezomib

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Treatment of adult patients with multiple myeloma
2. Treatment of adult patients with mantle cell lymphoma

B. Compendial Uses
1. Systemic light chain amyloidosis
2. Waldenström macroglobulinemia/lymphoplasmacytic lymphoma
3. Multicentric Castleman disease
4. Adult T-cell leukemia/lymphoma
5. Antibody mediated rejection of solid organ
6. Acute lymphoblastic leukemia
7. Follicular lymphoma
8. Kaposi sarcoma
9. Classic Hodgkin Lymphoma
10. POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) Syndrome
11. Peripheral T-cell Lymphomas
    a. Anaplastic large cell lymphoma
    b. Peripheral T-cell lymphoma not otherwise specified
    c. Angioimmunoblastic T-cell lymphoma
    d. Enteropathy-associated T-cell lymphoma
    e. Monomorphic epitheliotropic intestinal T-cell lymphoma
    f. Nodal peripheral T-cell lymphoma with TFH phenotype
    g. Follicular T-cell lymphoma
12. Breast implant-associated anaplastic large cell lymphoma (ALCL)
13. Hepatosplenic T-cell lymphoma
14. Mycosis fungoides/Sezary syndrome
15. AIDS-related B-cell lymphomas
    a. AIDS-related diffuse large B-cell lymphoma
    b. HHV8-positive diffuse large B-cell lymphoma not otherwise specified
    c. Primary effusion lymphoma
16. Desensitization therapy – heart transplant

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Multiple myeloma
Authorization of 12 months may be granted for the treatment of multiple myeloma.

B. Mantle cell lymphoma
Authorization of 12 months may be granted for the treatment of mantle cell lymphoma.

C. Multicentric Castleman disease
Authorization of 12 months may be granted for the treatment of multicentric Castleman disease as subsequent therapy.

D. Systemic light chain amyloidosis
Authorization of 12 months may be granted for the treatment of systemic light chain amyloidosis.

E. Waldenström macroglobulinemia/lymphoplasmacytic lymphoma
Authorization of 12 months may be granted for the treatment of Waldenström macroglobulinemia/lymphoplasmacytic lymphoma.

F. Peripheral T-cell lymphomas
Authorization of 12 months may be granted as a single agent for the treatment of any of the following peripheral T-cell lymphomas:
1. Anaplastic large cell lymphoma (ALCL)
2. Peripheral T-cell lymphoma not otherwise specified
3. Angioimmunoblastic T-cell lymphoma
4. Enteropathy-associated T-cell lymphoma
5. Monomorphic epitheliotropic intestinal T-cell lymphoma
6. Nodal peripheral T-cell lymphoma with TFH phenotype
7. Follicular T-cell lymphoma

G. Adult T-cell Leukemia/Lymphoma
Authorization of 12 months may be granted for the treatment of adult T-cell leukemia/lymphoma when the requested medication will be used as a single agent for subsequent therapy.

H. Breast implant-associated ALCL
Authorization of 12 months may be granted for the treatment of breast implant-associated ALCL when the requested medication will be used as a single agent for subsequent therapy.

I. Hepatosplenic T-cell lymphoma
Authorization of 12 months may be granted for the treatment of hepatosplenic T-cell lymphoma when the requested medication will be used as a single agent for refractory disease.

J. Mycosis fungoides/Sezary syndrome

Authorization of 12 months may be granted for the treatment of mycosis fungoides/Sezary syndrome when the requested medication will be used as a single agent for refractory disease.

K. AIDS-related B-cell lymphomas
Authorization of 12 months may be granted for the treatment of AIDS-related B-cell lymphomas when both of the following criteria are met:
1. The member has one of the following lymphomas:
    a. AIDS-related diffuse large B-cell lymphoma
    b. HHV8-positive diffuse large B-cell lymphoma, not otherwise specified
    c. Primary effusion lymphoma
2. The requested drug will be used as a component of bortezomib-ICE (ifosfamide, carboplatin, and etoposide)

L. Antibody mediated rejection of solid organ
Authorization of 12 months may be granted for the treatment of antibody mediated rejection of solid organ.

M. Acute lymphoblastic leukemia
Authorization of 12 months may be granted for the treatment of relapsed or refractory acute lymphoblastic leukemia.

N. Follicular Lymphoma
Authorization of 12 months may be granted for the treatment of relapsed or refractory follicular lymphoma.

O. Kaposi sarcoma
Authorization of 12 months may be granted for the treatment of Kaposi sarcoma as subsequent therapy.

P. Classic Hodgkin Lymphoma
Authorization of 12 months may be granted for the treatment of relapsed or refractory Classic Hodgkin Lymphoma.

Q. POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) Syndrome
Authorization of 12 months may be granted for treatment of POEMS syndrome in combination with dexamethasone.

R. Desensitization therapy – heart transplant
Authorization of 12 months may be granted for desensitization therapy for heart transplantation.

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested agent.

Authorization for 12 months may be granted when all of the following criteria are met:
A. The member is currently receiving therapy with the requested medication
B. The requested medication is being used to treat an indication enumerated in Section II
C. The member is receiving benefit from therapy. Benefit is defined as:
    1. No evidence of unacceptable toxicity while on the current regimen, and
    2. No evidence of disease progression while on the current regimen

IV. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:

1. The prescribing information for Velcade and bortezomib.
2. The available compendium
    a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
    b. Micromedex DrugDex
    c. American Hospital Formulary Service- Drug Information (AHFS-DI)
    d. Lexi-Drugs
    e. Clinical Pharmacology
3. NCCN Guideline: Waldenstrom Macroglobulinemia/Lymphoplasmacytic lymphoma
4. NCCN Guideline: Systemic light chain amyloidosis
5. NCCN Guideline: Multiple myeloma
6. NCCN Guideline: T-cell lymphomas
7. NCCN Guideline: Pediatric Hodgkin lymphoma
8. NCCN Guideline: Kaposi sarcoma
9. NCCN Guideline: Pediatric acute lymphoblastic leukemia
10. NCCN Guideline: B-cell lymphomas
11. NCCN Guideline: Acute lymphoblastic leukemia
12. Canadian Cardiovascular Society/Canadian Cardiac Transplant Network position statement on heart transplantation: patient eligibility, selection, and post-transplantation care
13. International Liver Transplantation Society consensus statement on immunosuppression in liver transplant recipients.
14. Review of bortezomib treatment of antibody-mediated rejection in renal transplantation

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Velcade are covered in addition to the following:

1. Systemic light chain amyloidosis
2. Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma
3. Multicentric Castleman's disease
4. Adult T-cell leukemia/lymphoma
5. Antibody-mediated rejection of solid organ
6. Acute lymphoblastic leukemia
7. Follicular lymphoma
8. Kaposi sarcoma
9. Classic Hodgkin lymphoma
10. POEMS syndrome
11. Peripheral T-cell lymphomas
    A. Anaplastic large cell lymphoma
    B. Peripheral T-cell lymphoma not otherwise specified
    C. Angioimmunoblastic T-cell lymphoma
    D. Enteropathy-associated T-cell lymphoma
    E. Monomorphic epitheliotropic intestinal T-cell lymphoma
    F. Nodal peripheral T-cell lymphoma with TFH phenotype
    G. Follicular T-cell lymphoma

12. Breast implant-associated anaplastic large cell lymphoma
13. Hepatosplenic T-cell lymphoma
14. Mycosis fungoides/Sezary syndrome
15. AIDS-related B-cell lymphomas
    1. AIDS-related diffuse large B-cell lymphoma
    2. HHV8-positive diffuse large B-cell lymphoma not otherwise specified
    3. Primary effusion lymphoma
16. Desensitization therapy- heart transplant

V. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information.

Support for using bortezomib to treat systemic light chain amyloidosis, Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma, multicentric Castleman's disease, adult T-cell leukemia/lymphoma, acute lymphoblastic leukemia, follicular lymphoma, Kaposi sarcoma, classic Hodgkin lymphoma, peripheral T-cell lymphoma, breast implant-associated anaplastic large cell lymphoma, hepatosplenic T-cell lymphoma, mycosis fungoides/Sezary syndrome, and AIDS-related B-cell lymphomas can be found in the NCCN Drugs and Biologics Compendium. Use of information in the NCCN Drugs and Biologics Compendium for off-label use of drugs and biologicals in an anti-cancer chemotherapeutic regimen is supported by the Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 (Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen).

Support for using bortezomib in the treatment of antibody mediated rejection can be found in the Canadian Cardiovascular Society and Canadian Cardiac Transplant Network position statement on heart transplantation: patient eligibility, selection, and post-transplantation care. The position statement indicates providers can consider adjunctive rituximab and/or bortezomib for treatment of antibody-mediated rejection.
Roberts et al conducted a systematic review to determine the efficacy of treatments for acute antibody-mediated rejection in kidney transplant recipients. The randomized studies were small (median, 13 patients/arm; range, 5-23), of which, four examined plasmapheresis (one suggested benefit) and one for immunoadsorption (also suggesting benefit). Marked heterogeneity was evident, including the definition and severity of AMR and the treatment regimen. The end point of graft survival was common to all studies. Small, nonrandomized controlled studies suggested benefit from rituximab or bortezomib. The effects of dose and regimen on the clinical response to any of the current treatments were not apparent from the available data. Data describing the efficacy of treatments for AMR in renal allografts are of low or very low quality. Larger randomized controlled trials and dose-response studies are required.
The International Liver Transplantation Society consensus statement on immunosuppression in liver transplant recipients states the treatment of moderate to severe AMR can include plasmapheresis with or without anti-B cell agents such as rituximab, bortezomib, or eculizumab (Quality/Certainty of Evidence: Moderate; Strength of Evidence: Conditional).

Support for using bortezomib as desensitization therapy to facilitate heart transplantation can be found in the Canadian Cardiovascular Society and Canadian Cardiac Transplant Network position statement on heart transplantation: patient eligibility, selection, and post-transplantation care. The position statement indicates intravenous immune globulin, rituximab and bortezomib form the foundation of desensitization treatments. Bortezomib should be considered if the patient has a poor response to rituximab desensitization therapy. Most pre transplantation desensitization protocols include IVIG 2 g/kg divided over 2 days (and continued monthly) with the additional use of rituximab in either a single 375 mg/m2 or 1 g dose. Effective B-cell depletion can be

assessed by measuring lymphocyte cell subsets 2 days post administration with target CD19 < 2%. If there is no reduction in antibody after 3 months, alternative therapies such as bortezomib and eculizumab may be considered. Concurrent plasmapheresis may be reserved for short-term antibody depletion peri-, intra-, and postoperatively.

Support for using bortezomib in POEMS syndrome can be found in the National Comprehensive Cancer Network's guideline for multiple myeloma. The NCCN Guideline for multiple myeloma supports the use of bortezomib in combination with dexamethasone as either induction therapy for transplant eligible patients or for transplant ineligible patients.

VI. REFERENCES

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