CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL ONCOLOGY

Brentuximab Vedotin (Adcetris®)

Version: 1.0

EFFECTIVE DATE: 1/1/2024

Please note the following:

Brentuximab Vedotin (Adcetris®)

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Brentuximab Vedotin (Adcetris): Discussion

Brentuximab vedotin is an anti-CD30 antibody conjugated via a protease-cleavable linker to the potent anti-microtubule agent monomethyl auristatin E (MMAE). Following binding to CD30, brentuximab vedotin is rapidly internalized and transported to lysosomes where MMAE is released and binds to tubulin, leading to cell cycle arrest and apoptosis. [1]

Therapy with brentuximab vedotin can cause tumor lysis syndrome in those with rapidly proliferating tumors and high tumor burden. Serious and opportunistic infections are possible and include progressive multifocal leukoencephalopathy (PML), serious dermatological reactions such as Stevens-Johnson syndrome, hematological toxicities and anaphylaxis and infusion reactions. [2]

Brentuximab vedotin (Adcetris) is approved by the Food and Drug Administration (FDA) for:

- Adult patients with previously untreated Stage III or IV classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vinblastine, and dacarbazine
- Pediatric patients 2 years and older with previously untreated high-risk classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide
- Adult patients with classical Hodgkin lymphoma (cHL) at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation
- Adult patients with classical Hodgkin lymphoma (cHL) after the failure of auto-HSCT or after the failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates
- Adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone

- Adult patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen
- Adult patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy [2]

The National Comprehensive Cancer Network (NCCN) endorses brentuximab vedotin in the following cancer types: B-cell lymphomas, Hodgkin lymphoma, pediatric aggressive mature B-cell lymphoma, pediatric Hodgkin lymphoma, primary cutaneous lymphoma, and T-cell lymphoma. [3,4,5,6,7,8]

Brentuximab Vedotin: Definitions

- **CD30 protein** - A protein found on some T cells and B cells (two types of white blood cells). It is a receptor for a protein called tumor necrosis factor, which is involved in cell growth and cell survival. The CD30 protein may be found in higher than normal amounts on some types of cancer cells, including lymphoma cells. The CD30 protein is a tumor marker. [9]
- **Deauville scale** - The five-point Deauville (D) scale is widely used to assess interim positron emission tomography (PET) metabolic response to chemotherapy in Hodgkin lymphoma (HL) patients. [10]
- F**ood and Drug Administration (FDA) -** The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- **Monomethyl auristatin E (MMAE) -** A very potent antimitotic agent that inhibits cell division by blocking the polymerization of tubulin.
- **National Comprehensive Cancer Network (NCCN) -** An alliance of thirty-two leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.

Brentuximab Vedotin: Policy

Brentuximab vedotin will be considered for coverage when the following criteria are met:

B-Cell Lymphoma
(diffuse large B-cell lymphoma, high-grade B-cell lymphoma, HIV-related B-cell lymphoma [primary effusion lymphoma, and HHV8-positive diffuse large B-cell lymphoma] and monomorphic post-transplant lymphoproliferative disorders [PTLD])

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Second-line and subsequent therapy if no intention to proceed to transplant for CD30+ disease for one of the following:
    a) Relapsed or refractory disease >12 months after completion of first-line therapy
    b) Primary refractory disease (partial response, no response, or progression) or relapsed disease <12 months after completion of first-line therapy if no intention to proceed to CAR T-cell therapy
    c) Alternative systemic therapy for relapsed/refractory disease if no intention to proceed to CAR T-cell therapy, if not previously used; OR
4. In combination with nivolumab for relapsed or refractory primary mediastinal large B-cell lymphoma (DLBCL only); OR
5. Component of brentuximab + CHP (cyclophosphamide, doxorubicin, prednisone) for CD30+ monomorphic PTLD (T-cell type) [3]

Hodgkin Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Primary treatment in combination with AVD (doxorubicin, vinblastine, dacarbazine) for stage III-IV disease (use with caution in patients >60 years of age; contraindicated in those with neuropathy); OR
4. Second-line or subsequent systemic therapy (if not previously used) for relapsed or refractory disease as a single agent or in combination with one of the following:
    a) Bendamustine
    b) ICE (ifosfamide, carboplatin, etoposide)
    c) Nivolumab for the treatment indications listed below:
        i. Relapsed or progressed disease after high dose therapy and autologous stem cell rescue (HDT/ASCR) ± brentuximab vedotin
        ii. Relapsed/refractory disease who are transplant-ineligible based on comorbidity or failure of second-line chemotherapy
        iii. Post-allogeneic transplant; OR
5. Maintenance therapy following high-dose therapy and autologous stem cell rescue (HDT/ASCR) for relapsed or refractory disease with a high risk of relapse and one of the following:
    a) Deauville score 1-3 prior to transplant
    b) Deauville score 4 prior to transplant; OR

Note: Patients with 2 or more of the following risk factors are considered high risk: remission duration less than 1 year, extranodal involvement, FDG-PET-positive response at time of transplant, B symptoms, and/or >1 second line/subsequent therapy regimen.

6. Primary treatment for adults age >60 years with one of the following:
    a) As a component of brentuximab vedotin followed by AVD (doxorubicin, vinblastine, dacarbazine) regimen conditionally followed by brentuximab vedotin

in responding patients with a complete or partial response for stage I-II unfavorable or stage III-IV disease
   b) Dacarbazine for stage I-II unfavorable or stage III-IV disease; OR
7. Palliative therapy as a single agent for relapsed or refractory disease for adults age >60 years of age [4]

Pediatric Aggressive Mature B-Cell Lymphoma - Primary Mediastinal Large B-Cell Lymphoma

1. Less than or equal to 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Consolidation/additional therapy if partial response is achieved for relapsed or refractory disease in combination with one of the following:
   a) Nivolumab
   b) Pembrolizumab [5]

Pediatric Hodgkin Lymphoma

1. Less than or equal to 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Primary treatment for high-risk disease as a component of one of the following:
   a) Bv-AVE-PC (brentuximab vedotin, doxorubicin, vincristine, etoposide, prednisone, cyclophosphamide)
   b) AEPA (brentuximab vedotin, etoposide, prednisone, doxorubicin); OR
4. Additional treatment for high-risk disease as a component of CAPDAC (cyclophosphamide, brentuximab vedotin, prednisone, dacarbazine) regimen following primary treatment with AEPA regimen; OR
5. Re-induction therapy in combination with involved site radiation therapy (ISRT) for highly favorable patients with relapsed or refractory, heavily pretreated disease (with platinum or anthracycline-based chemotherapy) OR if a decrease in cardiac function observed, in combination with one of the following:
   a) Bendamustine
   b) Nivolumab
   c) Gemcitabine; OR
6. Re-induction therapy or subsequent therapy (if not previously used) for relapsed or refractory disease as a consideration in patients with heavily pretreated disease (with platinum or anthracycline-based chemotherapy) or if a decrease in cardiac function observed, in combination with one of the following:
   a) Bendamustine
   b) Nivolumab
   c) Gemcitabine; OR
7. Maintenance therapy following high-dose therapy and autologous stem cell rescue (HDT/ASCR) for relapsed or refractory disease in select patients with high-risk disease

Note:

1. Highly favorable patients are those who may avoid ASCR: initial stage other than IIIB or IVB, no prior exposure to RT, duration of CR1 >1 year, absence of extranodal disease or B symptoms at relapse.

2. High-risk disease is any patient with progressive disease, refractory disease, or relapse within 1 year of original diagnosis.

Primary Cutaneous Lymphoma

Mycosis Fungoides/Sezary Syndrome

1) At least 18 years of age; AND
2) Prescribed by or in consultation with an oncologist; AND
3) Primary treatment for one of the following:
    a) Stage IB-IIA mycosis fungoides (MF), in combination with skin-directed therapy in selected cases
    b) Stage IIB MF with limited tumor lesions, with or without local radiation therapy
    c) Stage IIB MF with generalized tumor lesions, in combination with skin-directed therapy
    d) Stage III MF, in combination with skin-directed therapy
    e) Stage IVA1 or IVA2 Sezary syndrome, in combination with skin-directed therapy
    f) Stage IVA2 non-Sezary or stage IVB visceral disease (solid organ), with or without radiation therapy for local control
    g) Generalized cutaneous or extracutaneous lesions with large cell transformation (LCT), in combination with systemic therapy; OR
4) Subsequent treatment for one of the following:
    a) Stage IA mycosis fungoides (MF) that is refractory to multiple previous therapies, in combination with skin-directed therapy
    b) Stage IB-IIA MF in combination with skin-directed therapy
    c) Stage IIB MF with or without local radiation therapy for one of the following:
        i. Relapsed with T3 limited tumor lesions
        ii. Persistent with T1-3 limited tumor lesions
    d) Stage IIB MF in combination with skin-directed therapy for one of the following:
        i. Limited tumor lesions that are refractory to multiple previous therapies
        ii. Relapsed with T1-2 generalized tumor lesions
        iii. Relapsed with T3 generalized tumor lesions
        iv. Generalized tumor lesions that are refractory to multiple previous therapies
    e) Stage III MF that is refractory to multiple previous therapies, in combination with skin-directed therapy
    f) Relapsed or persistent stage IVA1 or IVA2 Sezary syndrome, in combination with skin-directed therapy
    g) Relapsed or persistent stage IVA2 non Sezary or stage IVB visceral disease (solid organ), with or without radiation therapy for local control
    h) Limited cutaneous lesions with large cell transformation (LCT) that is refractory to multiple previous therapies, in combination with skin-directed therapy
    i) Relapsed or persistent generalized cutaneous or extracutaneous lesions with LCT, in combination with skin-directed therapy

Note: Systemic therapies should be considered for patients with extensive skin involvement, higher skin disease burden, predominantly plaque disease, blood involvement, and/or inadequate response to skin-directed therapy.

Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Therapy for primary cutaneous anaplastic large cell lymphoma (ALCL) with multifocal lesions, or cutaneous ALCL with regional node (N1) (excludes systemic ALCL), as a single agent for one of the following:
    a) Primary treatment
    b) Relapsed/refractory disease; OR
4. Therapy for cutaneous anaplastic large cell lymphoma (ALCL) with regional node (N1) (excludes systemic ALCL) as a component of brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, prednisone) for one of the following:
    a) Primary treatment
    b) Relapsed/refractory disease; OR
5. Therapy for lymphomatoid papulosis (LyP) with extensive lesions as a single agent for relapsed/refractory disease following clinical trial, observation, retreatment with primary treatment, or treatment with an alternative regimen not used for primary treatment. [7]

Peripheral T-Cell Lymphomas

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Adult T-cell leukemia/lymphoma
    a) Used as a component of brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, prednisone) for CD30+ cases as one of the following:
        i. Chemotherapy in nonresponders to first-line therapy for chronic/smoldering subtype
        ii. First-line therapy for acute subtype OR lymphoma subtype
        iii. Continued treatment in responders to first-line therapy for acute subtype OR lymphoma subtype
    b) Second-line or subsequent therapy as a single agent for nonresponders to first-line therapy for acute or lymphoma subtypes (for CD30+ cases); OR
4. Breast implant-associated anaplastic large cell lymphoma (ALCL)
    a) Adjuvant systemic therapy for localized disease to capsule/implant/breast following incomplete excision or partial capsulectomy with residual disease if node-positive or radiation therapy is not feasible, or consider for extended disease (stage II-IV) as one of the following:
        i. Single-agent
        ii. Component of brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, prednisone)

b) Second-line and subsequent therapy for relapsed/refractory disease, as a single agent; OR

5. Extranodal NK/T-Cell Lymphoma - single agent for CD30+ relapsed/refractory disease following additional therapy with an alternate combination chemotherapy regimen (asparaginase-based) not previously used; OR
6. Hepatosplenic T-cell lymphoma for one of the following:
   a) Used as a component of brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, prednisone) for CD30+ cases as preferred first-line therapy OR consider for additional therapy if no response or progressive disease after first-line therapy as an alternate regimen if not previously used
   b) Single agent for CD30+ refractory disease after 2 first-line therapy regimens; OR
7. Peripheral T-cell lymphomas
   a) First-line therapy for stage I-IV ALK-positive anaplastic large cell lymphoma (ALCL) as a component of brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, prednisone)
   b) First-line therapy for stage III, IV ALK-positive anaplastic large cell lymphoma (ALCL) or stage I-IV ALK-negative ALCL as a component of brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, prednisone)
   c) Preferred first-line therapy for CD30+ stage I-IV peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) as a component of brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, prednisone) for one of the below disease types:
      i. Angioimmunoblastic T-cell lymphoma (AITL)
      ii. Enteropathy-associated T-cell lymphoma (EATL)
      iii. Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)
      iv. Nodal peripheral T-cell lymphoma with TFH phenotype (PTCL, TFH)
      v. Follicular T-cell lymphoma (FTCL), as a component of brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, prednisone)
   d) Second-line or initial palliative intent therapy and subsequent therapy for relapsed/refractory CD30+ peripheral T-cell lymphoma (PTCL), CD30+ angioimmunoblastic T-cell lymphoma (AITL), or anaplastic large cell lymphoma (ALCL), as a single agent [8]

Note: Coverage of brentuximab vedotin will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation OR when all criteria are met.

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Brentuximab Vedotin: References

1. Brentuximab vedotin. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3499340. Accessed July 12, 2023.
2. Brentuximab vedotin (Adcetris®) Package Insert https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125388s107lbl.pdf. Accessed July 12, 2023.
3. National Comprehensive Cancer Network Guidelines. B-Cell Lymphomas (Version 5.2023). https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed July 12, 2023.
4. National Comprehensive Cancer Network Guidelines. Hodgkin Lymphoma (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf. Accessed July 13, 2023
5. National Comprehensive Cancer Network Guidelines. Pediatric Aggressive Mature B-Cell Lymphomas (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/ped_b-cell.pdf. Accessed July 13, 2023.
6. National Comprehensive Cancer Network Guidelines. Pediatric Hodgkin Lymphoma (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/ped_hodgkin.pdf. Accessed July 14.2023.
7. National Comprehensive Cancer Network Guidelines. Primary Cutaneous Lymphomas (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf. Accessed July 14, 2023.
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9. National Cancer Institute. CD30 protein. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/cd30-protein. Accessed July 14, 2023.
10. Inter-Reader Reliability of Early FDG-PET/CT Response Assessment Using the Deauville Scale after 2 Cycles of Intensive Chemotherapy (OEPA) in Hodgkin's Lymphoma. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0149072. Accessed July 20, 2023.
11. What is Monomethyl Auristatin E (MMAE)? https://www.adcreview.com/the-review/what-is-monomethyl-auristatin-e-mmae/. Accessed July 19, 2023

Brentuximab Vedotin: Coding (CPT®, ICD 10 and HCPCS) *

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

CODE	DESCRIPTION
B20, C83.30-C83.39, C83.80-C83.89, C85.80-C85.89	B-Cell Lymphomas - HIV-Related B-Cell Lymphomas
C81.10-C81.19, C81.20-C81.29, C81.30-C81.39, C81.40-C81.49, C81.70-C81.79, C81.90-C81.99	Hodgkin Lymphoma – Adult and Pediatric
C83.30-C83.39, C85.20-C85.29, C83.90-C83.99	B-Cell Lymphomas - Diffuse Large B-Cell Lymphoma
C83.30-C83.39, C85.10 - C85.19	B-Cell Lymphomas - High-Grade B-Cell Lymphomas
C84.00-C84.09, C84.10-C84.19	Primary Cutaneous Lymphomas - Mycosis Fungoides/Sezary Syndrome
C84.40-C84.49, C84.60-C84.69, C84.70-C84.79, C86.2, C86.5	T-Cell Lymphomas - Peripheral T-Cell Lymphomas
C84.7A	T-Cell Lymphomas - Breast Implant-Associated ALCL
C84.90-C84.99, C84.Z0-C84.Z9, C86.0	T-Cell Lymphomas - Extranodal NK/T-Cell Lymphomas
C84.90-C84.99, C84.Z0-C84.Z9, C86.1	T-Cell Lymphomas - Hepatosplenic T-Cell Lymphoma
C85.20-C85.29	Pediatric Aggressive Mature B-Cell Lymphomas - Primary Mediastinal Large B-Cell Lymphoma
C86.6	Primary Cutaneous Lymphomas - Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders
C91.50, C91.51, C91.52	T-Cell Lymphomas - Adult T-Cell Leukemia/Lymphoma

D47.Z1	B-Cell Lymphomas - Post-Transplant Lymphoproliferative Disorders
J9042	Brentuximab vedotin (Adcetris)

Brentuximab Vedotin: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2024
2	Policy Review Dates:	11/9/2023
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee Approval Dates:	11/16/2023
6	Revision Changes:	