Medical Drug Clinical Criteria

Subject:	Adcetris (brentuximab vedotin)		
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Overview

This document addresses the use of Adcetris (brentuximab vedotin). Adcetris is a monoclonal antibody-drug conjugate (ADC) that consists of a chimeric IgG1 directed antibody against CD30 and a small molecule, monomethyl auristatin E (MMAE), a microtubule-disrupting agent. The anticancer activity is due to the binding of the ADC to CD30-expressing cells causing disruption of the microtubule network leading to cell death. Adcetris is FDA approved for certain patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma. The National Comprehensive Cancer Network (NCCN) provides additional recommendations with a category 2A level of evidence for the use of Adcetris.

Hodgkin Lymphoma (HL)

Adcetris was FDA approved in 2018 for previously untreated stage III or IV classical HL (cHL), in combination with chemotherapy. This FDA indication was updated later to read “in combination with doxorubicin, vinblastine, and dacarbazine”. NCCN gives additional combination options for older adults with untreated HL, including sequential therapy or in combination with dacarbazine or in combination with nivolumab. It is also FDA approved for pediatric individuals 2 years of age and older with previously untreated high risk cHL, in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide. For relapsed HL, Adcetris is approved as a single agent after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or after failure of at least two prior multi-agent chemotherapy regimens when individuals were ineligible for transplant. In the relapsed setting, NCCN recommends Adcetris alone or in combination with bendamustine or nivolumab, or in combination with ifosfamide, carboplatin, etoposide; and regardless of individual’s eligibility for transplant. It is also approved as post-auto-HSCT consolidation therapy for those at high risk of relapse or progression. NCCN recommends as maintenance therapy for 1 year if brentuximab naïve and Deauville score less than 5.

Non-Hodgkin Lymphoma (NHL)

NHLs are a broad and diverse group of malignancies affecting both B- and T-lymphocytes. Adcetris is mostly used for T-Cell Lymphomas. These can broadly be classified as cutaneous or non-cutaneous. Cutaneous T-cell lymphomas include mycosis fungoides (MF) and sezary syndrome (SS), lymphomatoid papulosis (LyP), and the cutaneous form of anaplastic large cell lymphoma (ALCL), known as primary cutaneous ALCL. “Non-cutaneous” T-cell lymphomas are diverse and NCCN divides the treatment algorithms into certain types such as peripheral t-cell lymphoma (PTCL), Adult T-cell leukemia/lymphoma (ATLL), breast implant-associated ALCL, extranodal NK/T-Cell lymphoma, nasal type (NKTL), and hepatosplenic T-Cell Lymphoma (HSTCL). Subtypes of PTCLs include but are not limited to PTCL-NOS (not-otherwise-specified), systemic ALCL, and angioimmunoblastic t-cell lymphoma.

Adcetris is FDA approved for *relapsed* primary cutaneous ALCL and CD30 expressing MF. NCCN recommends it also as first-line treatment of primary cutaneous ALCL and MF/SS when there is advanced disease presentation (which would disease that is stage IIB or higher, large cell transformation, extensive skin involvement, higher skin disease burden, primarily plaque disease, blood involvement, or inadequate response to skin-directed therapy). NCCN also recommends Adcetris for relapsed/refractory LyP with extensive lesions. Adcetris is also FDA approved to treat relapsed systemic ALCL after failure of at least one prior multi-agent chemotherapy regimen. In the area of relapsed disease, NCCN also recommends Adcetris for PTCL, angioimmunoblastic t-cell lymphoma, NKTL, HTL, and breast implant-associated ALCL. NCCN also recommends Adcetris as adjuvant therapy for breast implant-associated ALCL.

Adcetris is also FDA approved in combination cyclophosphamide, doxorubicin, and prednisone (CHP) for previously untreated CD30 expressing PTCL and systemic ALCL (which is a type of PTCL) based on the results of the ECHELON-2 study (Horwitz 2018). Study inclusion criteria states “newly diagnosed CD30+ mature T-cell lymphomas”. NCCN additionally recommends this front-line regimen for patients with ATLL and the following types of PTCL: angioimmunoblastic t-cell lymphoma, enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, nodal peripheral T-cell lymphoma with TFH phenotype, follicular T-cell lymphoma. NCCN also recommends Adcetris as secondary treatment for ATLL and for relapsed or refractory Primary Mediastinal Large B-Cell Lymphoma in combination with pembrolizumab.

Adcetris (brentuximab vedotin) has a black box warning for John Cunningham (JC) virus infection resulting in progressive multifocal leukoencephalopathy (PML). Fatal cases of JC virus infection resulting in PML have been reported in individuals receiving Adcetris.

Definitions and Measures

Adjuvant therapy: Treatment given after the primary treatment to increase the chances of a cure; may include chemotherapy, radiation, hormone or biological therapy.

Autologous stem cells: Stem cells harvested from the individual's own bone marrow or peripheral blood.

Consolidation: Repetitive cycles of treatment during the immediate post-remission period; used especially for leukemia; also known as intensification therapy.

Deauville Score: 5-point rating scale used in staging and response of HL and NHL; visual assessment of F-fluorodeoxyglucose (FDG) uptake in the involved sites. Score of 5 indicates markedly higher uptake initially involved site and/or new lesions.
High-dose or myeloablative chemotherapy (HDC): The administration of cytotoxic agents using doses several times greater than the standard therapeutic dose.

Line of Therapy:

- First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
- Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.

Maintenance therapy: Designed to maintain a condition to prevent a relapse.

Mycosis fungoides: A sub-type of cutaneous T-cell lymphoma in which tumor cells invade the skin causing reddening (erythroderma) and/or plaques. There may also be involvement of lymph nodes, blood, and internal organs.

One line of therapy: Single line of therapy.

Refractory Disease: Illness or disease that does not respond to treatment.

Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.

Sézary Syndrome: A sub-type of cutaneous T-cell lymphoma characterized by itching and redness with T cell leukemia whose cells clonally match those invading the skin. Sézary Syndrome has historically been more difficult to treat than mycosis fungoides.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Adcetris (brentuximab)

Requests for Adcetris (brentuximab vedotin) may be approved if the following criteria are met:

I. Individual has a diagnosis of Hodgkin Lymphoma (HL); **AND**
II. Individual is using for one of the following:
    A. Previously untreated ~~stage III or IV~~ classical HL, in combination with one of the following (Label, NCCN 2A)
        1. Doxorubicin, vinblastine, and dacarbazine; **OR**
        2. Etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD regimen); **OR**
    B. ~~Previously untreated~~ Primary treatment classical HL in older adults (≥60 years), as sequential therapy with doxorubicin, vinblastine, and dacarbazine, or in combination with dacarbazine (NCCN 2A); **OR**
    C. Primary treatment for classical HL in older adults (≥60 years) in combination with nivolumab; **OR**
    ~~C.~~D. Previously untreated high risk classical HL, in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide; **OR**
    ~~D.~~E. Relapsed or refractory disease ~~in a single line of therapy~~ as a single agent or in combination with bendamustine or nivolumab (Label, NCCN 2A); **OR**
    ~~E.~~F. Relapsed or refractory disease ~~as second or subsequent line of therapy~~ in combination with ifosfamide, carboplatin, etoposide; **OR**

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~~F.~~G. As consolidation therapy after an autologous stem cell transplantation for individuals at high risk of relapse or progression~~, defined as individuals with any of the following:~~
   ~~1. Primary refractory HL; **OR**~~
   ~~2. Relapsed HL with an initial remission duration of less than 12 months; **OR**~~
   ~~3. Extranodal involvement at the start of pre-transplantation salvage chemotherapy;~~

OR

~~G.~~H. As maintenance therapy for 1 year following high-dose therapy and autologous stem cell rescue for relapsed or refractory disease in those who are brentuximab vedotin naïve and have a Deauville score of less than 5 (NCCN 2A);

OR

III. Individual has a diagnosis of pediatric Hodgkin Lymphoma; **AND**

IV. Individual is using for one of the following:
   A. Primary, subsequent, or maintenance treatment for high-risk disease (high risk defined as progressive disease, refractory disease, or relapse within 1 year of original diagnosis) (Label, NCCN 1, 2A); **OR**
   B. Treatment for relapsed or refractory disease as a single agent or in combination with bendamustine, nivolumab, or gemcitabine (NCCN 2A, DP B2a);~~.~~

OR

V. Individual has a diagnosis of CD30+ Non-Hodgkin Lymphoma;
   AND

VI. Individual is using for one of the following primary cutaneous lymphomas (Label, NCCN 2A):
   A. Cutaneous anaplastic large cell lymphoma; **OR**
   B. Relapsed or refractory lymphomatoid papulosis; **OR**
   C. Mycosis fungoides/Sézary syndrome;
   OR

VII. Individual is using for one of the following T-Cell lymphomas:
   A. Peripheral T-cell lymphoma (including anaplastic large cell lymphoma, peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, nodal peripheral T-cell lymphoma with TFH phenotype, follicular T-cell lymphoma) (Label, NCCN 2A); **OR**
   B. Adult T-cell leukemia/lymphoma (NCCN 2A)l **OR**
   C. Systemic anaplastic large cell lymphoma (Label); **OR**
   D. Relapsed or refractory Extranodal NK/T-Cell lymphomas (NCCN 2A); **OR**
   E. Refractory Hepatosplenic T-Cell lymphoma (NCCN 2A); **OR**
   F. Breast implant-associated anaplastic large cell lymphoma (NCCN 2A); **OR**
   OR

VIII. Individual is using for one of the following B-Cell lymphomas (NCCN 2A):
   A. Relapsed or refractory Pediatric (18 years or younger) Primary Mediastinal Large B-Cell Lymphoma; in combination with pembrolizumab or nivolumab; **OR**
   B. Relapsed or refractory Diffuse Large B-Cell Lymphomas (DLBCL), including DLBCL arising from indolent lymphoma; **OR**
   C. Relapsed or refractory monomorphic Post-Transplant lymphoproliferative disorders (B-cell type); **OR**
   D. Relapsed or refractory High-grade B-Cell Lymphomas; **OR**
   E. Relapsed or refractory HIV-related B-Cell Lymphoma; **OR**
   ~~E.~~F. Relapsed or refractory plasmablastic lymphoma.

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Requests for Adcetris (brentuximab vedotin) may not be approved when the above criteria are not met and for all other indications.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J9042	Injection, brentuximab vedotin, 1 mg [Adcetris]

ICD-10 Diagnosis

B20	Human Immunodeficiency virus [HIV] disease (when specified as HIV related B-cell lymphoma)
C81.00-C81.99	Hodgkin lymphoma
C83.30-C83.3~~89~~	Diffuse large B-cell lymphoma
C84.00-C84.19	Mycosis fungoides, Sézary disease
C84.40-C84.49	Peripheral T-cell lymphoma, not classified

C84.60-C84.69	Anaplastic large cell lymphoma, ALK-positive
C84.70-C84.79	Anaplastic large cell lymphoma, ALK-negative
C84.7A	Anaplastic large cell lymphoma, ALK-negative, breast
~~C84.A0-C84.A9~~	~~Cutaneous T-cell lymphoma, unspecified~~
C84.Z0-C84.Z9	Other mature T/NK-cell lymphomas
C85.20-C85.29	Mediastinal (thymic) large B-cell lymphoma
~~C86.1~~	~~Hepatosplenic T-cell lymphoma~~
~~C86.2~~	~~Enteropathy-type (intestinal) T-cell lymphoma~~
~~C86.5~~	~~Angioimmunoblastic T-cell lymphoma~~
~~C86.6~~	~~Primary cutaneous CD30-positive T-cell proliferations~~
C86.00	Extranodal NT/T-cell lymphoma, nasal type not having achieved remission
C86.10	Hepatosplenic T-cell lymphoma not having achieved remission
C86.20	Enteropathy-type (intestinal) T-cell lymphoma not having achieved remission
C86.50	Angioimmunoblastic T-cell lymphoma not having achieved remission
C86.60	Primary cutaneous CD30-positive T-cell proliferations not having achieved remission
C91.50-C91.52	Adult T-cell lymphoma/leukemia (HTLV-1-associated) not having achieved remission
~~C91.51~~	~~Adult T-cell lymphoma/leukemia (HTLV-1-associated), in remission~~
~~C91.52~~	~~Adult T-cell lymphoma/leukemia (HTLV-1-associated), in relapse~~
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)
Z85.71	Personal history of Hodgkin lymphoma
Z85.72	Personal history of non-Hodgkin lymphomas

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Document History

Revised: 05/16/2025
Document History:

- 05/16/2025 – Annual Review: Add use in plasmablastic lymphoma per NCCN; Add combination use with nivolumab for Pediatric (18 years or younger) Primary Mediastinal Large B-Cell Lymphoma and as Primary treatment for classical Hodgkin Lymphoma (HL) in older adults; remove stage requirements, single line of therapy requirements, and definition of high risk of progression in HL criteria for simplicity and to align with NCCN; wording and formatting updates. Coding Reviewed: Removed ICD-10-CM C86.1, C86.2, C86.5, C86.6, C84.A0-C84.A9. Removed C83.39 from code range to leave C83.30-C83.38. Added ICD-10-CM C86.10, C86.20, C86.50, C86.60, C83.398, C86.00, C83.80-C83.89. Consolidated C91.50, C91.51 and C91.52 into one code range and updated description.
- 05/17/2024 – Annual Review: Simplify non-Hodgkin lymphoma criteria and add HIV-related b-cell lymphoma and update Primary Mediastinal Large B-Cell Lymphoma to include combination with pembrolizumab instead of nivolumab; remove pembrolizumab combination in Hodgkin lymphoma as not recommended by NCCN; add additional combination regimen for previously untreated Hodgkin lymphoma per NCCN; include maintenance therapy and therapy for relapsed/refractory disease as a single agent in pediatric Hodgkin lymphoma. Coding Reviewed: Added ICD-10-CM B20, C83.30-C83.39, C84.7A, D47.Z1.
- 11/17/2023 – Select Review – Formatting. Coding Reviewed: No changes.
- 05/19/2023 – Annual Review: for HL: add pembrolizumab and ICE combination, for NHL:add b-cell lymphoma and subsequent therapy , add peds HL. Coding Reviewed: No changes.
- 03/13/2023 – Select Review: Update criteria to include NCCN 2A recommendation for use in Primary Mediastinal Large B-Cell Lymphoma in combination with nivolumab. Coding Reviewed: Added ICD-10-CM C85.20-C85.29.
- 12/12/2022 – Select Review: Update criteria to include new FDA approved indication for previously untreated high risk classical Hodgkin Lymphoma, in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide. Coding Reviewed: Removed ICD-10-CM C91.50-C51.52. Added ICD-10-CM C91.50, C91.51, C91.52.
- 05/20/2022 – Annual Review: Update Non-hodgkin lymphoma section to list specific examples of T-cell lymphoma, include additional examples per NCCN 2A recommendations; simplify criteria for Adult T-cell lymphoma; update mycosis fungoides/Sézary syndrome criteria for definition of advanced disease per NCCN; remove untreated Hepatosplenic T-cell lymphoma as NCCN 2B; add combination with nivolumab for relapsed or refractory Hodgkin lymphoma per NCCN. Coding Reviewed: No changes.
- 05/21/2021 – Annual Review: No changes. Coding Reviewed: No changes.
- 05/15/2020 – Annual Review: Add additional regimens for older adults with classical Hodgkin Lymphoma; update adult T-cell leukemia language to align with NCCN. Coding reviewed: No changes.
- 05/17/2019 – Annual Review: First review of Adcetris clinical criteria. Add criteria for previously untreated adult T-cell leukemia/lymphoma and hepatosplenic gamma-delta T-cell lymphoma. Add references for off label indications. Coding Reviewed: Added ICD-10 DX code range C84.Z0-C84.Z9.

References

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: April 8, 2025.
2. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.

3. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc. Updated periodically.
4. Cole PD, McCarten KM, Pei Q, et al. Brentuximab vedotin with gemcitabine for pediatric and young adult patients with relapsed or refractory Hodgkin's Lymphoma (AHOD1221): a Children's Oncology Group, multicentre single-arm, phase 1-2 trial. Lancet Oncol 2018; 19:1229-1238.
5. Cole PD, Mauz-Korholz C, Mascarin M, et al. Nivolumab and brentuximab vedotin (BV)-based, response-adapted treatment in children, adolescents, and young adults (CAYA) with standard-risk relapsed/refractory classical Hodgkin Lymphoma (R/R cHL): Primary analysis. J Clin Oncol 2020;38:8013 [Abstract].
6. Harker-Murray P, Mauz-Körholz C, Leblanc TM, et al. Nivolumab, Brentuximab Vedotin, +/- Bendamustine For R/R Hodgkin Lymphoma in Children, Adolescents, and Young Adults [published online ahead of print, 2022 Dec 23]. Blood. 2022;blood.2022017118. doi:10.1182/blood.2022017118.
7. Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet. 2019;393(10168):229-240.
8. Herrera AF, Moskowitz AJ, Bartlett NL, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. Blood 2018; 131: 1183-1194. [NCT02572167].
9. Jacobsen ED, Sharman JP, Oki Y, et al. Brentuximab vedotin demonstrates objective responses in a phase 2 study of relapsed/refractory DLBCL with variable CD30 expression. Blood 2015; 125:1394-1402.
10. Lynch RC, Cassaday RD, Smith SD, et al. Dose-dense brentuximab vedotin plus ifosfamide, carboplatin, and etoposide for second-line treatment of relapsed or refractory classical Hodgkin lymphoma: a single centre, phase 1/2 study. Lancet Haematol. 2021;8(8):e562-e571. doi:10.1016/S2352-3026(21)00170-8.
11. O'Connor OA, Lue JK, Sawas A, et al. Brentuximab vedotin plus bendamustine in relapsed or refractory Hodgkin's lymphoma: an international, multicentre, single-arm, phase 1-2 trial [published correction appears in Lancet Oncol. 2018 Mar;19(3):e137]. Lancet Oncol. 2018;19(2):257-266. doi:10.1016/S1470-2045(17)30912-9.
12. NCCN Clinical Practice Guidelines in Oncology. © 2025 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed April 2025.
    a. B-Cell Lymphomas. V2.2025. Revised February 10, 2025.
    b. Hodgkin Lymphoma. V2.2025. Revised January 30, 2025.
    c. Pediatric Aggressive Mature B-Cell Lymphomas. V1.2025. Revised April 3, 2025.
    d. Pediatric Hodgkin lymphoma. V1.2024. Revised May 14, 2024.
    e. Primary Cutaneous Lymphomas. V2.2025. Revised April 1, 2025.
    f. T-Cell Lymphomas. V1.2025. Revised November 11, 2024.