

Adcetris® (brentuximab vedotin) (Intravenous)

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I. Length of Authorization ^{1,5,7,15,18,21}

Coverage will be provided for 6 months and may be renewed (unless otherwise specified).

- Treatment of previously untreated Pediatric Classical Hodgkin Lymphoma (cHL) as a component of Bv-AVE-PC (brentuximab vedotin, doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide) has a maximum of 5 doses.
- Pediatric cHL as a component of AEPA (brentuximab vedotin, etoposide, prednisone, doxorubicin) has a maximum of 2 cycles (6 doses).
- Pediatric cHL as a component of CAPDAC (cyclophosphamide, brentuximab vedotin, prednisone, dacarbazine) has a maximum of 4 cycles (8 doses).
- Pediatric and Adult cHL in combination with nivolumab has a maximum of 4 doses.
- Adult cHL in combination with bendamustine has a maximum of 6 doses.
- Adult cHL in combination with ifosfamide, carboplatin, and etoposide (ICE) has a maximum of 4 doses.
- Adult cHL in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD) has a maximum of 6 doses.
- Adult cHL post-auto HSCT, Primary Cutaneous Lymphomas, and Pediatric cHL (excluding use with Bv-AVE-PC, AEPA, CAPDAC, or nivolumab) has a maximum of 16 doses.
- Treatment of previously untreated Adult Stage III or IV cHL in combination with AVD (doxorubicin, vinblastine, and dacarbazine) has a maximum of 12 doses.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Adcetris 50 mg single-dose vial: 9 vials every 28 days

B. Max Units (per dose and over time) [HCPCS Unit]:

Classical Hodgkin Lymphoma:

- 450 billable units every 28 days

Primary Cutaneous Lymphomas:

- 200 billable units every 21 days

All other indications:

- 200 billable units every 21 days

III. Initial Approval Criteria ¹

Coverage is provided in the following conditions:

- Patient is at least 18 years of age (unless otherwise specified); **AND**

Universal Criteria ¹

- Patient must not be receiving concomitant bleomycin; **AND**
- Patient does not have severe renal impairment (i.e., CrCl <30 mL/min); **AND**
- Patient does not have moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment; **AND**
- Patient has CD30-positive disease; **AND**

Adult Classic Hodgkin Lymphoma (cHL) † ^{1,2,4,12-14}

- Used as single agent therapy; **AND**
 - Used as consolidation/maintenance therapy post-autologous hematopoietic stem cell transplant (auto-HSCT) in patients at high risk* for relapse or progression † ‡; **OR**
 - Patient has relapsed disease after failure of auto-HSCT or after failure of at least 2 (two) prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates †; **OR**
 - Used as subsequent systemic therapy (if not previously used) for relapsed or refractory disease ‡; **OR**
 - Used as palliative therapy for relapsed or refractory disease ‡; **AND**
 - Patient is > 60 years of age; **OR**
 - Patient has poor performance status; **OR**
 - Patient has substantial comorbidities; **OR**
- Used in combination with bendamustine; **AND**
 - Used as subsequent systemic therapy (if not previously used) for relapsed or refractory disease ‡; **OR**
- Used in combination with nivolumab; **AND**

- Used as subsequent systemic therapy (if not previously used) for relapsed or refractory disease ‡; **OR**
- Used in combination with dacarbazine; **AND**
 - Used as primary treatment in patients with low ejection fraction ‡; **AND**
 - Patient is > 60 years of age; **OR**
 - Patient has poor performance status; **OR**
 - Patient has substantial comorbidities; **OR**
- Used in combination with ifosfamide, carboplatin, and etoposide (ICE); **AND**
 - Used as subsequent systemic therapy (if not previously used) for relapsed or refractory disease ‡; **OR**
- Used in combination with doxorubicin, vinblastine, and dacarbazine (AVD); **AND**
 - Used as initial therapy for previously untreated stage III or IV disease †; **OR**
 - Used as primary treatment for stage II unfavorable disease with no neuropathy ‡; **AND**
 - Patient is > 60 years of age; **OR**
 - Patient has poor performance status; **OR**
 - Patient has substantial comorbidities; **OR**
- Used in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD); **AND**
 - Used as primary treatment for stage III-IV disease; **AND**
 - Patient is 18-61 years of age

**High risk for relapse or progression may be defined as:*

- *Refractory disease, disease relapse within 12 months, or relapse ≥12 months with extranodal disease following frontline therapy; **OR***
- *Two or more of the following: remission duration <1 year, extranodal involvement, FDG-PET+ response at time of transplant, B symptoms, and/or >1 second-line/subsequent therapy regimen*

Pediatric Classic Hodgkin Lymphoma (cHL) † ‡ Φ^{1,2,24,26,23e}

- Patient is ≤ 18 years of age*; **AND**
 - Used as re-induction or subsequent therapy (if not previously used); **AND**
 - Patient has relapsed or refractory disease; **AND**
 - Used in combination with nivolumab or gemcitabine; **AND**
 - Used in patients heavily pretreated with platinum or anthracycline-based chemotherapy; **OR**
 - Used if a decrease in cardiac function is observed; **OR**
 - Used as primary therapy in patients with high risk disease**; **AND**

- Used as a component of AEPA (brentuximab vedotin, etoposide, prednisone, doxorubicin) regimen; **OR**
- Used as a component of Bv-AVE-PC (brentuximab vedotin, doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide) †; **AND**
 - Patient is at least 2 years of age; **OR**
- Used as additional treatment following primary treatment with AEPA regimen in patients with high risk disease**; **AND**
 - Used as a component of CAPDAC (cyclophosphamide, brentuximab vedotin, prednisone, dacarbazine) regimen

**Pediatric Hodgkin Lymphoma may be applicable to adolescent and young adult (AYA) patients up to the age of 39 years.*

***High risk disease may be defined as: Stage IIB with bulk or E-lesions (involvement of extra-lymphatic tissue), Stage IIIA with bulk AND E-lesions, or Stage IIIB or IV disease.*

T-Cell Lymphomas ^{1-3,15,16}

- Peripheral T-Cell Lymphomas (PTCL)
 - Used as a single agent for relapsed or refractory disease as subsequent therapy for one of the following:
 - Systemic Anaplastic Large Cell Lymphoma (sALCL) † Φ
 - Peripheral T-Cell Lymphoma not otherwise specified (PTCL-NOS) ‡
 - Angioimmunoblastic T-cell Lymphoma (AITL) ‡; **OR**
 - Used in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) in patients with CD30 expression ≥ 10% per immunohistochemistry (IHC) as initial therapy for previously untreated:
 - Systemic Anaplastic Large Cell Lymphoma (sALCL) † Φ
 - Peripheral T-Cell Lymphoma (PTCL) not otherwise specified †
 - Angioimmunoblastic T-cell Lymphoma (AITL) †

Primary Cutaneous Lymphomas ^{1,2,17}

- Mycosis Fungoides (MF) † Φ/Sezary Syndrome (SS) ‡
 - Used as single agent systemic therapy; **AND**
 - Used as subsequent therapy; **AND**
 - Patient has CD30 expression ≥ 5% per IHC
- Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders ‡ Φ
 - Used as a single agent in patients previously treated with systemic therapy; **AND**

- Patient has primary cutaneous anaplastic large cell lymphoma (pcALCL) † Φ; **OR**
- Patient has lymphomatoid papulosis (LyP) with extensive lesions that is relapsed or refractory to all treatment options (e.g., clinical trial, observation, retreatment with primary treatment, or treatment with alternative regimen not used for primary treatment)

B-Cell Lymphomas ‡^{2,11}

- Diffuse Large B-Cell Lymphoma (DLBCL)
 - Used as a single agent as subsequent therapy if no intention to proceed to transplant; **AND**
 - Used for relapsed disease >12 months after completion of first-line therapy; **OR**
 - Used for primary refractory disease (partial response, no response, or progression) or relapsed disease <12 months after completion of first-line therapy*; **OR**
 - Used as alternative systemic therapy (if not previously used) for relapsed/refractory disease*

**Note: Only applies to patients which are non-candidates for CAR T-cell therapy.*

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Φ Orphan Drug

IV. Renewal Criteria¹

Coverage may be renewed based upon the following criteria:

- Patient continues to meet the universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Disease response with treatment defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: peripheral neuropathy, anaphylaxis and infusion reactions, hematologic toxicities (thrombocytopenia, neutropenia and anemia), serious infections, opportunistic infections, tumor lysis syndrome, hepatotoxicity, pulmonary toxicity, serious dermatologic reactions, gastrointestinal complications, uncontrolled hyperglycemia, etc.; **AND**
- Patient has been evaluated for the presence of progressive multifocal leukoencephalopathy (PML) and has been found to be negative; **AND**

Pediatric cHL (in combination with Bv-AVE-PC, AEPA, CAPDAC, or nivolumab)

- Coverage may not be renewed.

Pediatric cHL (all other treatment settings/regimens)

- Patient has not exceeded a maximum of 16 (sixteen) doses.

Adult cHL (in combination with nivolumab, bendamustine, ICE , BrECADD)

- Coverage may not be renewed.

Adult cHL (post-auto HSCT consolidation)

- Patient has not exceeded a maximum of 16 (sixteen) doses.

Adult cHL (previously untreated stage III or IV in combination with AVD)

- Patient has not exceeded a maximum of 12 (twelve) doses.

Primary Cutaneous Lymphomas

- Patient has not exceeded a maximum of 16 (sixteen) doses.

V. Dosage/Administration [1,5,7,15,18-21,23, 25-31,35-36](#)

Indication	Dose
Adult cHL	<p><u>Previously untreated stage III or IV in combination with doxorubicin, vinblastine, and dacarbazine (AVD)</u> Administer 1.2 mg/kg (up to 120 mg) by intravenous infusion every 2 weeks until a maximum of 12 doses, disease progression, or unacceptable toxicity</p> <p><u>Consolidation post auto HSCT as a single agent</u> Administer 1.8 mg/kg (up to 180 mg) by intravenous infusion every 3 weeks until a maximum of 16 cycles, disease progression, or unacceptable toxicity</p> <p><u>Relapsed disease in combination with bendamustine</u> Administer 1.8 mg/kg (up to 180 mg) by intravenous infusion every 3 weeks for a maximum of 6 doses</p> <p><u>Relapsed disease in combination with nivolumab</u> Administer 1.8 mg/kg (up to 180 mg) by intravenous infusion every 3 weeks for a maximum of 4 doses</p> <p><u>Relapsed disease in combination with ifosfamide, carboplatin, and etoposide (ICE)</u></p>

	<p>Administer 1.5 mg/kg (up to 150 mg) by intravenous infusion on day 1 and 8 every 3 weeks for a maximum of 4 doses</p> <p><u>Primary therapy in combination with dacarbazine</u></p> <p>Administer 1.8 mg/kg (up to 180 mg) by intravenous infusion every 3 weeks in combination for 12 doses, followed by monotherapy until disease progression or unacceptable toxicity</p> <p><u>Primary therapy in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD)</u></p> <p>Administer 1.8 mg/kg (up to 180 mg) by intravenous infusion every 3 weeks for a maximum of 6 cycles</p> <p><u>All other treatment settings/regimens:</u></p> <p>Administer 1.8 mg/kg (up to 180 mg) by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity</p>
<p>Primary Cutaneous Lymphomas</p>	<p><u>Single agent therapy for Mycosis Fungoides (MF)/Sezary Syndrome (SS)</u></p> <p>Administer 1.8 mg/kg (up to 180 mg) by intravenous infusion every 3 weeks until a maximum of 16 cycles, disease progression, or unacceptable toxicity</p> <p><u>Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders</u></p> <p>Administer 1.8 mg/kg (up to 180 mg) by intravenous infusion every 3 weeks until a maximum of 16 cycles, disease progression, or unacceptable toxicity</p>
<p>Pediatric cHL</p>	<p><u>Previously untreated high-risk disease in combination with Bv-AVE-PC (doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide)</u></p> <p>Administer 1.8 mg/kg (up to 180 mg) by intravenous infusion every 3 weeks for a maximum of 5 doses</p> <p><u>Primary therapy for high-risk disease as a component of AEPA (brentuximab vedotin, etoposide, prednisone, doxorubicin)</u></p> <p>Administer 1.2 mg/kg (up to 120 mg) by intravenous infusion on days 1, 8, 15 every 28 days for 2 cycles</p> <p><u>Additional treatment as a component of CAPDAC (cyclophosphamide, brentuximab vedotin, prednisone, dacarbazine)</u></p> <p>Administer 1.2 mg/kg (up to 120 mg) by intravenous infusion on days 1 and 8 every 21 days for 4 cycles</p> <p><u>In combination with nivolumab</u></p>

	Administer 1.8 mg/kg (up to 180 mg) by intravenous infusion every 3 weeks for a maximum of 4 doses <u>All other treatment settings/regimens</u> Administer 1.8 mg/kg (up to 180 mg) by intravenous infusion every 3 weeks until a maximum of 16 cycles, disease progression, or unacceptable toxicity
All other indications	Administer 1.8 mg/kg (up to 180 mg) by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity

VI. Billing Code/Availability Information

HCPCS Code:

- J9042 – Injection, brentuximab vedotin, 1 mg; 1 billable unit = 1 mg

NDC:

- Adcetris 50 mg powder for injection in a single-dose vial: 51144-0050-xx

VII. References (STANDARD)

1. Adcetris [package insert]. Bothell, WA; Seagen, Inc; June 2023. Accessed April 2024.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for brentuximab vedotin. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed April 2024.
3. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) T-Cell Lymphomas. Version 3.2024. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed April 2024.
4. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Hodgkin Lymphoma, Version 3.2024. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed April 2024.
5. Duvoc M, Tetzlaff MT, Gangar P, et al. Results of a Phase II trial of brentuximab vedotin for CD30+ cutaneous T-cell lymphoma and lymphomatoid papulosis. J Clin Oncol 2015; 33:3759-65.

6. Horwitz SM, Advani RH, Bartlett NL, et al. Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin. *Blood* 2014;123:3095-3100.
7. Alderuccio, JP., Desai, A., Yepes, M.M., et al. Frontline brentuximab vedotin in breast implant-associated anaplastic large-cell lymphoma. *Clin Case Rep* 2018; 6(4): 634-637. doi:10.1002/ccr3.1382.
8. Fahrenbruch R, Kintzel P, Bott AM, et al. Dose Rounding of Biologic and Cytotoxic Anticancer Agents: A Position Statement of the Hematology/Oncology Pharmacy Association. *J Oncol Pract*. 2018 Mar;14(3):e130-e136.
9. Hematology/Oncology Pharmacy Association (Updated January 2022). *Intravenous Cancer Drug Waste Issue Brief*. Retrieved from https://www.hoparx.org/documents/65/HOPA_Drug_Waste_Issue_Brief_-_Updated_01.19.22_FINAL.pdf
10. Bach PB, Conti RM, Muller RJ, et al. Overspending driven by oversized single dose vials of cancer drugs. *BMJ*. 2016 Feb 29;352:i788.
11. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) B-Cell Lymphomas, Version 1.2024. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed April 2024.
12. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma [published correction appears in *N Engl J Med*. 2018 Mar 1;378(9):878]. *N Engl J Med*. 2018;378(4):331-344.
13. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2015;385(9980):1853-1862.
14. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol*. 2012;30(18):2183-2189.
15. 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.
16. Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol*. 2012;30(18):2190-2196.

17. Prince HM, Kim YH, Horwitz SM, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. *Lancet*. 2017;390(10094):555-566.
18. Cole PD, McCarten KM, Pei Q, et al. Brentuximab vedotin with gemcitabine for paediatric 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 Sep;19(9):1229-1238. doi: 10.1016/S1470-2045(18)30426-1. Epub 2018 Aug 16.
19. 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 Feb 26;125(9):1394-402. Doi: 10.1182/blood-2014-09-598763. Epub 2015 Jan 8.
20. Chang VA, Wang HY, Reid EG. Activity of brentuximab vedotin in AIDS-related primary effusion lymphoma. *Blood Adv*. 2019 Mar 12;3(5):766-768. Doi: 10.1182/bloodadvances.2018026351.
21. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Pediatric Aggressive Mature B-Cell Lymphomas. Version 1.2024. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed April 2024.
22. Zinzani PL, Pellegrini C, Chiappella A, et al. Brentuximab vedotin in relapsed primary mediastinal large B-cell lymphoma: results from a phase 2 clinical trial. *Blood*. 2017 Apr 20;129(16):2328-2330. doi: 10.1182/blood-2017-01-764258.
23. Zinzani PL, Santoro A, Gritti G, et al. Nivolumab Combined With Brentuximab Vedotin for Relapsed/Refractory Primary Mediastinal Large B-Cell Lymphoma: Efficacy and Safety From the Phase II CheckMate 436 Study. *J Clin Oncol*. 2019 Nov 20;37(33):3081-3089. doi: 10.1200/JCO.19.01492.
24. Castellino SM, Pei Q, Parsons SK, et al. Brentuximab Vedotin with Chemotherapy in Pediatric High-Risk Hodgkin's Lymphoma. *N Engl J Med*. 2022 Nov 3;387(18):1649-1660. doi: 10.1056/NEJMoa2206660.
25. Cole PD, Mauz-Körholz 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.
26. Harker-Murray P, Mauz-Körholz C, Leblanc T, et al. Nivolumab and brentuximab vedotin with or without bendamustine for R/R Hodgkin lymphoma in children, adolescents, and young adults. *Blood*. 2023 Apr 27;141(17):2075-2084. doi: 10.1182/blood.2022017118. PMID: 36564047.

27. O'Connor OA, Lue JK, Sawas A, et al. Brentuximab vedotin plus bendamustine in relapsed or refractory Hodgkin's lymphoma: an international, multicenter, single-arm, phase 1-2 trial. *Lancet Oncol* 2018;19:257-266.
28. 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:e562-e571.
29. Friedberg JW, Forero-Torres A, Bordoni RE, et al. Frontline brentuximab vedotin in combination with dacarbazine or bendamustine in patients aged ≥ 60 years with HL. *Blood* 2017;130:2829-2837.
30. Friedberg JW, Forero-Torres A, Holkova B, et al. Long-term follow-up of brentuximab vedotin \pm dacarbazine as first line therapy in elderly patients with Hodgkin lymphoma [abstract]. *J Clin Oncol* 2018;36 (Suppl 15):Abstract 7542.
31. Advani RH, Moskowitz AJ, Bartlett NL, et al. Brentuximab vedotin in combination with nivolumab in relapsed or refractory Hodgkin lymphoma: 3-year study results. *Blood* 2021;138:427-438
32. Borchmann P, Moccia AA, Greil R, et al. BreECADD Is non-inferior to eBEACOPP in patients with advanced stage classical Hodgkin Lymphoma: Efficacy results of the GHSG Phase III HD21 trial. *Hematological Oncology* 2023;41:881-882.
33. Eichenauer DA, Plütschow A, Kreissl S, et al. Incorporation of brentuximab vedotin into first-line treatment of advanced classical Hodgkin's lymphoma: final analysis of a phase 2 randomised trial by the German Hodgkin Study Group. *Lancet Oncol.* 2017 Dec;18(12):1680-1687. doi: 10.1016/S1470-2045(17)30696-4. Epub 2017 Nov 10. PMID: 29133014.
34. Evens AM, Advani RH, Helenowski IB, et al. Multicenter Phase II Study of Sequential Brentuximab Vedotin and Doxorubicin, Vinblastine, and Dacarbazine Chemotherapy for Older Patients With Untreated Classical Hodgkin Lymphoma. *J Clin Oncol.* 2018 Oct 20;36(30):3015-3022. doi: 10.1200/JCO.2018.79.0139. Epub 2018 Sep 4.
35. Aubrais R, Bouabdallah K, Chartier L, et al. Salvage therapy with brentuximab-vedotin and bendamustine for patients with R/R PTCL: a retrospective study from the LYSA group. *Blood Adv.* 2023 Oct 10; 7(19): 5733–5742. Published online 2022 Dec 10. doi: 10.1182/bloodadvances.2022008524
36. Metzger ML, Link MP, Billett AL, et al. Excellent Outcome for Pediatric Patients With High-Risk Hodgkin Lymphoma Treated With Brentuximab Vedotin and Risk-Adapted Residual Node Radiation. *J Clin Oncol.* 2021 Jul 10;39(20):2276-2283. doi: 10.1200/JCO.20.03286. Epub 2021 Apr 7. PMID: 33826362; PMCID: PMC8260923.

VIII. References (ENHANCED)

- 1e. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Primary Cutaneous Lymphomas, Version 2.2024. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®.

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- 2e. Gopal AK, Chen R, Smith SE, et al. Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. *Blood*. 2015;125(8):1236–1243.
- 3e. Chen RW, Palmer J, Martin, et al. Results of a Phase II Trial of Brentuximab Vedotin As First Line Salvage Therapy in Relapsed/Refractory HL Prior to AHCT [abstract]. *Blood* 2014;124:Abstract 501.
- 4e. 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. *Lancet Oncol* 2018; 19:257.
- 5e. Friedberg JW, Forero-Torres A, Bordoni RE, et al. Frontline brentuximab vedotin in combination with dacarbazine or bendamustine in patients aged ≥60 years with HL. *Blood*. 2017 Dec 28;130(26):2829-2837.
- 6e. Friedberg JW, Forero-Torres A, Holkova B, et al. Long-term follow-up of brentuximab vedotin ± dacarbazine as first line therapy in elderly patients with Hodgkin lymphoma [abstract]. *J Clin Oncol* 2018;36 (Suppl 15): Abstract 7542.
- 7e. Pro B, Advani R, Brice P, et al. Five-year results of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma [published correction appears in *Blood*. 2018 Jul 26;132(4):458-459]. *Blood*. 2017;130(25):2709–2717.
- 8e. Johnson L, O'Donoghue JM, McLean N, et al. Breast implant associated anaplastic large cell lymphoma: The UK experience. Recommendations on its management and implications for informed consent. *Eur J Surg Oncol*. 2017 Aug;43(8):1393-1401.
- 9e. Ishida T, Joh T, Uike N, et al. Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. *J Clin Oncol*. 2012 Mar 10;30(8):837-42.
- 10e. Ishida T, Utsunomiya A, Jo T, et al. Mogamulizumab for relapsed adult T-cell leukemia-lymphoma: Updated follow-up analysis of phase I and II studies. *Cancer Sci*. 2017;108(10):2022–2029.
- 11e. Kwong YL, Chang TSY, Tan D, et al. PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. *Blood* 2017; 129:2437-2442.
- 12e. Kim YH, Tavallaee M, Sundram U, et al. Phase II Investigator-Initiated Study of Brentuximab Vedotin in Mycosis Fungoides and Sézary Syndrome With Variable CD30 Expression Level: A Multi-Institution Collaborative Project. *J Clin Oncol*. 2015;33(32):3750–3758.
- 13e. 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 Feb 26;125(9):1394-402.

- 14e. Chang VA, Wang HY, Reid EG. Activity of brentuximab vedotin in AIDS-related primary effusion lymphoma. *Blood Adv.* ;3(5):766–768.
- 15e. 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(11):1183–1194.
- 16e. Evens AM, Advani RH, Helenowski IB, et al. Multicenter Phase II Study of Sequential Brentuximab Vedotin and Doxorubicin, Vinblastine, and Dacarbazine Chemotherapy for Older Patients With Untreated Classical Hodgkin Lymphoma. *J Clin Oncol.* 2018;36(30):3015-3022.
- 17e. 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. *Lancet Oncol.* 2018 Feb;19(2):257-266.
- 18e. Cole PD, Mauz-Körholz 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(15_suppl):8013-8013.
- 19e. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Pediatric Hodgkin Lymphoma, Version 2.2023. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed April 2024.
- 20e. Metzger ML, Link MP, Billett AL, et al. Excellent Outcome for Pediatric Patients With High-Risk Hodgkin Lymphoma Treated With Brentuximab Vedotin and Risk-Adapted Residual Node Radiation. *J Clin Oncol.* 2021 Jul 10;39(20):2276-2283.
- 21e. 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 Aug;8(8):e562-e571.
- 22e. Armand P, Rodig S, Melnichenko V, et al. Pembrolizumab in Relapsed or Refractory Primary Mediastinal Large B-Cell Lymphoma. *J Clin Oncol.* 2019 Dec 1;37(34):3291-3299.
- 23e. Harker-Murray P, Mauz-Körholz C, Leblanc T, et al. Nivolumab and brentuximab vedotin with or without bendamustine for R/R Hodgkin lymphoma in children, adolescents, and young adults. *Blood.* 2023;141(17):2075-2084.
- 24e. Prime Therapeutics Management. Adcetris Clinical Literature Review Analysis. Last updated April 2024. Accessed April 2024.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C81.10	Nodular sclerosis Hodgkin lymphoma, unspecified site
C81.11	Nodular sclerosis Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.12	Nodular sclerosis Hodgkin lymphoma, intrathoracic lymph nodes
C81.13	Nodular sclerosis Hodgkin lymphoma, intra-abdominal lymph nodes
C81.14	Nodular sclerosis Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.15	Nodular sclerosis Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.16	Nodular sclerosis Hodgkin lymphoma, intrapelvic lymph nodes
C81.17	Nodular sclerosis Hodgkin lymphoma, spleen
C81.18	Nodular sclerosis Hodgkin lymphoma, lymph nodes of multiple sites
C81.19	Nodular sclerosis Hodgkin lymphoma, extranodal and solid organ sites
C81.20	Mixed cellularity Hodgkin lymphoma, unspecified site
C81.21	Mixed cellularity Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.22	Mixed cellularity Hodgkin lymphoma, intrathoracic lymph nodes
C81.23	Mixed cellularity Hodgkin lymphoma, intra-abdominal lymph nodes
C81.24	Mixed cellularity Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.25	Mixed cellularity Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.26	Mixed cellularity Hodgkin lymphoma, intrapelvic lymph nodes
C81.27	Mixed cellularity Hodgkin lymphoma, spleen
C81.28	Mixed cellularity Hodgkin lymphoma, lymph nodes of multiple sites
C81.29	Mixed cellularity Hodgkin lymphoma, extranodal and solid organ sites
C81.30	Lymphocyte depleted Hodgkin lymphoma, unspecified site
C81.31	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.32	Lymphocyte depleted Hodgkin lymphoma, intrathoracic lymph nodes
C81.33	Lymphocyte depleted Hodgkin lymphoma, intra-abdominal lymph nodes
C81.34	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.35	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.36	Lymphocyte depleted Hodgkin lymphoma, intrapelvic lymph nodes
C81.37	Lymphocyte depleted Hodgkin lymphoma, spleen
C81.38	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of multiple sites
C81.39	Lymphocyte depleted Hodgkin lymphoma, extranodal and solid organ sites
C81.40	Lymphocyte-rich Hodgkin lymphoma, unspecified site
C81.41	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of head, face, and neck

ICD-10	ICD-10 Description
C81.42	Lymphocyte-rich Hodgkin lymphoma, intrathoracic lymph nodes
C81.43	Lymphocyte-rich Hodgkin lymphoma, intra-abdominal lymph nodes
C81.44	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.45	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.46	Lymphocyte-rich Hodgkin lymphoma, intrapelvic lymph nodes
C81.47	Lymphocyte-rich Hodgkin lymphoma, spleen
C81.48	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of multiple sites
C81.49	Lymphocyte-rich Hodgkin lymphoma, extranodal and solid organ sites
C81.70	Other Hodgkin lymphoma unspecified site
C81.71	Other Hodgkin lymphoma lymph nodes of head, face, and neck
C81.72	Other Hodgkin lymphoma intrathoracic lymph nodes
C81.73	Other Hodgkin lymphoma intra-abdominal lymph nodes
C81.74	Other Hodgkin lymphoma lymph nodes of axilla and upper limb
C81.75	Other Hodgkin lymphoma lymph nodes of inguinal region and lower limb
C81.76	Other Hodgkin lymphoma intrapelvic lymph nodes
C81.77	Other Hodgkin lymphoma spleen
C81.78	Other Hodgkin lymphoma lymph nodes of multiple sites
C81.79	Other Hodgkin lymphoma extranodal and solid organ sites
C81.90	Hodgkin lymphoma, unspecified, unspecified site
C81.91	Hodgkin lymphoma, unspecified, lymph nodes of head, face and neck
C81.92	Hodgkin lymphoma, unspecified, intrathoracic lymph nodes
C81.93	Hodgkin lymphoma, unspecified, intra-abdominal lymph nodes
C81.94	Hodgkin lymphoma, unspecified, lymph nodes of axilla and upper limb
C81.95	Hodgkin lymphoma, unspecified, lymph nodes of inguinal region and lower limb
C81.96	Hodgkin lymphoma, unspecified, intrapelvic lymph nodes
C81.97	Hodgkin lymphoma, unspecified, spleen
C81.98	Hodgkin lymphoma, unspecified, lymph nodes of multiple sites
C81.99	Hodgkin lymphoma, unspecified, extranodal and solid organ sites
C83.30	Diffuse large B-cell lymphoma unspecified site
C83.31	Diffuse large B-cell lymphoma, lymph nodes of head, face, and neck
C83.32	Diffuse large B-cell lymphoma intrathoracic lymph nodes
C83.33	Diffuse large B-cell lymphoma intra-abdominal lymph nodes

ICD-10	ICD-10 Description
C83.34	Diffuse large B-cell lymphoma lymph nodes of axilla and upper limb
C83.35	Diffuse large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.36	Diffuse large B-cell lymphoma intrapelvic lymph nodes
C83.37	Diffuse large B-cell lymphoma, spleen
C83.38	Diffuse large B-cell lymphoma lymph nodes of multiple sites
C83.39	Diffuse large B-cell lymphoma extranodal and solid organ sites
C84.00	Mycosis fungoides, unspecified site
C84.01	Mycosis fungoides, lymph nodes of head, face and neck
C84.02	Mycosis fungoides, intrathoracic lymph nodes
C84.03	Mycosis fungoides, intra-abdominal lymph nodes
C84.04	Mycosis fungoides, lymph nodes of axilla and upper limb
C84.05	Mycosis fungoides, lymph nodes of inguinal region and lower limb
C84.06	Mycosis fungoides, intrapelvic lymph nodes
C84.07	Mycosis fungoides, spleen
C84.08	Mycosis fungoides, lymph nodes of multiple sites
C84.09	Mycosis fungoides, extranodal and solid organ sites
C84.10	Sézary disease, unspecified site
C84.11	Sézary disease, lymph nodes of head, face, and neck
C84.12	Sézary disease, intrathoracic lymph nodes
C84.13	Sézary disease, intra-abdominal lymph nodes
C84.14	Sézary disease, lymph nodes of axilla and upper limb
C84.15	Sézary disease, lymph nodes of inguinal region and lower limb
C84.16	Sézary disease, intrapelvic lymph nodes
C84.17	Sézary disease, spleen
C84.18	Sézary disease, lymph nodes of multiple sites
C84.19	Sézary disease, extranodal and solid organ sites
C84.40	Peripheral T-cell lymphoma, not classified, unspecified site
C84.41	Peripheral T-cell lymphoma, not classified, lymph nodes of head, face and neck
C84.42	Peripheral T-cell lymphoma, not classified, intrathoracic lymph nodes
C84.43	Peripheral T-cell lymphoma, not classified, intra-abdominal lymph nodes
C84.44	Peripheral T-cell lymphoma, not classified, lymph nodes of axilla and upper limb
C84.45	Peripheral T-cell lymphoma, not classified, lymph nodes of inguinal region of lower limb

ICD-10	ICD-10 Description
C84.46	Peripheral T-cell lymphoma, not classified, intrapelvic lymph nodes
C84.47	Peripheral T-cell lymphoma, not classified, spleen
C84.48	Peripheral T-cell lymphoma, not classified, lymph nodes of multiple sites
C84.49	Peripheral T-cell lymphoma, not classified, extranodal and solid organ sites
C84.60	Anaplastic large cell lymphoma, ALK-positive, unspecified site
C84.61	Anaplastic large cell lymphoma, ALK-positive, lymph nodes of head, face and neck
C84.62	Anaplastic large cell lymphoma, ALK-positive, intrathoracic lymph nodes
C84.63	Anaplastic large cell lymphoma, ALK-positive, intra-abdominal lymph nodes
C84.64	Anaplastic large cell lymphoma, ALK-positive, lymph nodes of axilla and upper limb
C84.65	Anaplastic large cell lymphoma, ALK-positive, lymph nodes of inguinal region and lower limb
C84.66	Anaplastic large cell lymphoma, ALK-positive, intrapelvic lymph nodes
C84.67	Anaplastic large cell lymphoma, ALK-positive, spleen
C84.68	Anaplastic large cell lymphoma, ALK-positive, lymph nodes of multiple sites
C84.69	Anaplastic large cell lymphoma, ALK-positive, extranodal and solid organ sites
C84.70	Anaplastic large cell lymphoma, ALK-negative, unspecified site
C84.71	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of head, face and neck
C84.72	Anaplastic large cell lymphoma, ALK-negative, intrathoracic lymph nodes
C84.73	Anaplastic large cell lymphoma, ALK-negative, intra-abdominal lymph nodes
C84.74	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of axilla and upper limb
C84.75	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of inguinal region and lower limb
C84.76	Anaplastic large cell lymphoma, ALK-negative, intrapelvic lymph nodes
C84.77	Anaplastic large cell lymphoma, ALK-negative, spleen
C84.78	Anaplastic large cell lymphoma, ALK-negative, lymph nodes of multiple sites
C84.79	Anaplastic large cell lymphoma, ALK-negative, extranodal and solid organ sites
C85.20	Mediastinal (thymic) large B-cell lymphoma, unspecified site
C85.21	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of head, face and neck
C85.22	Mediastinal (thymic) large B-cell lymphoma, intrathoracic lymph nodes
C85.23	Mediastinal (thymic) large B-cell lymphoma, intra-abdominal lymph nodes
C85.24	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of axilla and upper limb
C85.25	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C85.26	Mediastinal (thymic) large B-cell lymphoma, intrapelvic lymph nodes
C85.27	Mediastinal (thymic) large B-cell lymphoma, spleen

ICD-10	ICD-10 Description
C85.28	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of multiple sites
C85.29	Mediastinal (thymic) large B-cell lymphoma, extranodal and solid organ sites
C86.5	Angioimmunoblastic T-cell lymphoma
C86.6	Primary cutaneous CD30-positive T-cell proliferations
Z85.71	Personal history of Hodgkin lymphoma
Z85.72	Personal history of non-Hodgkin lymphomas

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: <https://www.cms.gov/medicare-coverage-database/search.aspx>. Additional indications, including any preceding information, may be applied at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	Applicable State/US Territory	Contractor
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC