Department:	Utilization Management	**Original Approval:**	10/12/2012
Policy #:	PM105	**Last Approval:**	03/08/2019
Title:	Brentuximab vedotin (Adcetris®) for injection, for intravenous use		
Approved By:	UM Pharmacy Subcommittee		

BACKGROUND

Brentuximab vedotin is a CD30-directed antibody-drug conjugate indicated for treatment of patients with:

- Previously untreated Stage 3 or 4 cHL: Adult patients with newly diagnosed Stage 3 or 4 classical Hodgkin lymphoma (cHL) in combination with chemotherapy (adriamycin, vinblastine, and dacarbazine)
- Consolidation therapy in cHL: Adult patients with cHL at high risk of coming back or becoming worse after a stem cell transplant (SCT)
- Relapsed cHL: Adult patients with cHL after an SCT fails or after at least 2 combination chemotherapy treatments fail and SCT is not an option
- Previously untreated sALCL or other CD30-expressing PTCL: Adult patients with newly diagnosed 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 chemotherapy (cyclophosphamide, doxorubicin, and prednisone)
- Relapsed sALCL: Adult patients with sALCL after at least 1 combination chemotherapy treatment fails
- Relapsed pcALCL or CD30-expressing MF: Adult patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy (treatment that reaches and affects the entire body) [1]

CD30 is a member of the tumor necrosis factor receptor family. CD30 is expressed on the surface of sALCL cells and on Hodgkin Reed-Sternberg (HRS) cells in classical HL, and has limited expression on healthy tissue and cells. In vitro data suggest that signaling through CD30-CD30L binding may affect cell survival and proliferation.[1]

Brentuximab vedotin is an antibody-drug conjugate (ADC), wherein the antibody is a chimeric IgG1 directed against CD30. The small molecule, MMAE, is a microtubule disrupting agent. MMAE is covalently attached to the antibody via a linker. Nonclinical data suggest that the anticancer activity of ADCETRIS is due to the binding of the ADC to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cells. Additionally, in vitro data provide evidence for antibody dependent cellular phagocytosis (ADCP).[1]

The recommended dose is 1.8 mg/kg up to a maximum of 180 mg, administered as an intravenous infusion over 30 minutes every 3 weeks, with dose adjustments with mild hepatic impairment.[1]

CONDITIONS WITH APPROVAL

Each authorization period will be for **twelve months**.

All requests for brentuximab vedotin (Adcetris) also require referral to CHPW Case Management.

INDICATIONS/CRITERIA

Medicaid Members	***Continue to criteria for approval below.***
Medicare Members	***Step-utilization of Part D drugs not required.***

Brentuximab vedotin is considered medically necessary for any of the following indications:

National Comprehensive Cancer Network (NCCN) Category for Brentuximab vedotin[2]

NCCN Categories of Evidence and Consensus: **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.[2]

NCCN Disease	NCCN Recommended Use	NCCN Category
B-Cell Lymphomas - Follicular Lymphoma (grade 1-2)	Treatment of histologic transformation to CD30+ diffuse large B-cell lymphoma in patients who have received multiple lines of chemoimmunotherapy for indolent or transformed disease	2A
B-Cell Lymphomas - Histologic Transformation of Marginal Zone Lymphoma to Diffuse Large B-Cell Lymphoma	Treatment of patients who have received multiple lines of chemoimmunotherapy for indolent or transformed disease	2A
B-Cell Lymphomas - Diffuse Large B-Cell Lymphoma	Second-line or subsequent therapy for partial response, no response, relapsed, progressive, or refractory CD30+ disease in non-candidates for transplant	2A

B-Cell Lymphomas - Diffuse Large B-Cell Lymphoma	Second-line or subsequent therapy for partial response, no response, relapsed, progressive, or refractory CD30+ primary cutaneous diffuse large B-cell lymphoma, leg type in non-candidates for transplant	2A
B-Cell Lymphomas - High-Grade B-Cell Lymphomas	Second-line or subsequent therapy for partial response, no response, relapsed, progressive, or refractory CD30+ disease in non-candidates for transplant	2A
B-Cell Lymphomas – AIDS-Related B-Cell Lymphomas	Second-line or subsequent therapy for relapse of CD30+ AIDS-related diffuse large B-cell lymphoma, primary effusion lymphoma, and HHV8-positive diffuse large B-cell lymphoma, not otherwise specified (NOS) in noncandidates for high-dose therapy	2A
B-Cell Lymphomas - Post-Transplant Lymphoproliferative Disorders	Second-line and subsequent therapy for patients with partial response, persistent or progressive disease after receiving chemoimmunotherapy as first-line treatment for CD30+ monomorphic PTLD (B-cell type)	2A
Hodgkin Lymphoma - Classic Hodgkin Lymphoma (Age ≥18 years)	Primary treatment in combination with AVD (doxorubicin, vinblastine, dacarbazine) for stage III-IV disease	2A if no known neuropathy and either International Prognostic Score (IPS) ≥4 or bleomycin contraindicated 2B for all others
Hodgkin Lymphoma - Classic Hodgkin Lymphoma (Age ≥18 years)	Second-line or subsequent systemic therapy for relapsed or refractory disease as a single agent or as a component of DHAP (dexamethasone, cisplatin, high-dose cytarabine) + brentuximab vedotin • ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin) + brentuximab vedotin • Gemcitabine/bendamustine/vinorelbine + brentuximab vedotin • GVD (gemcitabine, vinorelbine, liposomal doxorubicin) + brentuximab vedotin • ICE (ifosfamide, carboplain, etoposide) + brentuximab vedotin • IGEV (ifosfamide, gemcitabine, vinorelbine) + brentuximab vedotin	2A

Hodgkin Lymphoma - Classic Hodgkin Lymphoma (Age ≥18 years)	Maintenance therapy following high-dose therapy and autologous stem cell rescue (HDT/ASCR) for relapsed or refractory disease for patients with high risk* of relapse • if Deauville 1-3 prior to transplant • if Deauville 4 prior to transplant *Patients with 2 or more of the following risk factors are considered high risk: remission duration less than 1 year, extranodal involvement, PET+ response at time of transplant, B symptoms, and/or >1 salvage regimen	2A
Hodgkin Lymphoma - Classic Hodgkin Lymphoma in Older Adults (Age >60 years)	Palliative therapy as a single agent for relapsed or refractory disease	2A
Primary Cutaneous Lymphomas - Mycosis Fungoides/Sezary Syndrome	Preferred systemic therapy as primary treatment for •stage IA mycosis fungoides (MF) with B1 blood involvement, with or without skin-directed therapy •stage IB-IIA MF with a higher disease burden (eg, predominantly plaque disease), with or without skin-directed therapy •stage IIB MF with limited tumor lesions, with or without local radiation therapy •stage IIB MF with generalized tumor lesions, with or without skin-directed therapy •stage III MF, with or without skin-directed therapy •stage IV Sezary syndrome	2A for all others 2B for stage IA MF with B1 blood involvement
Primary Cutaneous Lymphomas - Mycosis Fungoides/Sezary Syndrome	Systemic therapy as primary treatment for •stage IA mycosis fungoides (MF) with B1 blood involvement, with or without skin-directed therapy •stage IB-IIA MF with a higher disease burden (eg, predominantly plaque disease) and B1 blood involvement, with or without skin-directed therapy •stage IIB MF with generalized tumor lesions, with or without skin-directed therapy (preferred) •stage III MF, with or without skin-directed therapy •stage IV Sezary syndrome, with or without skin-directed therapy •stage IV non-Sezary or visceral disease (solid organ), with or without radiation therapy for local control (preferred) •large cell transformation (LCT) with generalized cutaneous or extracutaneous lesions, with or without skin-directed therapy (preferred)	2A for all others 2B for stage IA MF with B1 blood involvement

Primary Cutaneous Lymphomas - Mycosis Fungoides/Sezary Syndrome	Preferred systemic therapy as treatment for •stage IA mycosis fungoides (MF) with B1 blood involvement that is relapsed, persistent, or refractory to multiple previous therapies, with or without skin-directed therapy •relapsed or persistent stage IB-IIA MF with a higher disease burden (eg, predominantly plaque disease), with or without skin-directed therapy •relapsed or persistent stage IIB MF with limited tumor lesions, with or without local radiation therapy •stage IIB MF with limited tumor lesions refractory to multiple previous therapies, with or without skin-directed therapy •relapsed or persistent stage IIB MF with generalized tumor lesions, with or without skin-directed therapy •stage IIB MF with generalized tumor lesions refractory to multiple previous therapies •relapsed or persistent stage III MF, with or without skin-directed therapy •stage III MF that is refractory to multiple previous therapies •relapsed or persistent stage IV Sezary syndrome •relapsed or persistent stage IV non Sezary or visceral disease (solid organ), with or without radiation therapy for local control •large cell transformation (LCT) with limited cutaneous lesions that is refractory to multiple previous therapies •relapsed or persistent LCT with generalized cutaneous or extracutaneous lesions, with or without skin-directed therapy	2A for all others 2B for relapsed or persistent stage IA MF with B1 blood involvement
Primary Cutaneous Lymphomas - Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders	Therapy for primary cutaneous anaplastic large cell lymphoma (ALCL) with multifocal lesions, or cutaneous ALCL with regional nodes (excludes systemic ALCL), as a single agent for •primary treatment (preferred) •relapsed/refractory disease	2A
Primary Cutaneous Lymphomas - Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders	Therapy for cutaneous anaplastic large cell lymphoma (ALCL) with regional nodes (excludes systemic ALCL) as a component of brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, prednisone) for •primary treatment •relapsed/refractory disease	2A
Primary Cutaneous Lymphomas - Primary	Therapy for lymphomatoid papulosis (LyP) with extensive lesions as a single agent for	2A

Cutaneous CD30+ T-Cell Lymphoproliferative Disorders	relapsed/refractory disease following clinical trial, observation, retreatment with primary treatment, or treatment with alternative regimen not used for primary treatment	
T-Cell Lymphomas - Peripheral T-Cell Lymphomas	Preferred first-line therapy for stage I, II ALK-positive anaplastic large cell lymphoma as a component of brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, prednisone)	1 for 6 cycles ± ISRT 2B for 3-4 cycles + ISRT
T-Cell Lymphomas - Peripheral T-Cell Lymphomas	Preferred first-line therapy for stage III, IV ALK-positive anaplastic large cell lymphoma as a component of brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, prednisone)	1
T-Cell Lymphomas - Peripheral T-Cell Lymphomas	Preferred first-line therapy for CD30+ stage I-IV peripheral T-cell lymphoma not otherwise specified, ALK-negative anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma, enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, nodal peripheral T-cell lymphoma with TFH phenotype, or follicular T-cell lymphoma, as a component of brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, prednisone)	2A
T-Cell Lymphomas - Peripheral T-Cell Lymphomas	Preferred second-line and subsequent therapy for relapsed/refractory anaplastic large cell lymphoma, CD30+ peripheral T-cell lymphoma, or CD30+ angioimmunoblastic T-cell lymphoma, as a single agent	2A
T-Cell Lymphomas - Breast Implant-Associated ALCL	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 a single agent •as a component of brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, prednisone)	2A
T-Cell Lymphomas - Adult T-Cell Leukemia/Lymphoma	Used as a component of brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, prednisone) for CD30+ cases as •chemotherapy in nonresponders to first-line therapy for chronic/smoldering subtype •first-line therapy for acute subtype •continued treatment in responders to first-line therapy for acute subtype •first-line therapy for lymphoma subtype	2A

	•continued treatment in responders to first-line therapy for lymphoma subtype	
T-Cell Lymphomas - Adult T-Cell Leukemia/Lymphoma	Preferred second-line or subsequent therapy as a single agent for nonresponders to first-line therapy for acute or lymphoma subtypes (for CD30 expressing cases)	2A
T-Cell Lymphomas - Extranodal NK/T-Cell Lymphoma, nasal type	Preferred therapy as a single agent for CD30+ relapsed/refractory disease following additional therapy with an alternate combination chemotherapy regimen (asparaginase-based) not previously used	2A
T-Cell Lymphomas - Hepatosplenic Gamma-Delta T-Cell Lymphoma	Used a component of brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, prednisone) for CD30+ cases •as preferred primary treatment •consider as an alternate induction regimen if not used in primary treatment	2A
T-Cell Lymphomas - Hepatosplenic Gamma-Delta T-Cell Lymphoma	Preferred second-line and subsequent therapy as a single agent for CD30+ refractory disease after 2 primary treatment regimens	2A

SPECIAL CONSIDERATIONS

Boxed Warning for Progressive Multifocal Leukoencephalopathy (PML). JC virus infection resulting in PML and death has been reported in ADCETRIS-treated patients. First onset of symptoms occurred at various times from initiation of ADCETRIS therapy, with some cases occurring within 3 months of initial exposure. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider the diagnosis of PML in any patient presenting with newonset signs and symptoms of central nervous system abnormalities. Hold ADCETRIS dosing for any suspected case of PML and discontinue ADCETRIS dosing if a diagnosis of PML is confirmed.

Contraindications per the Adcetris Prescribing Information include(s): Concomitant use with bleomycin due to pulmonary toxicity.

LIMITATIONS/EXCLUSIONS

Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

CFR		
WAC		
RCW		
Contract Citation	☐ WAH	
	☐ IMC	
	☐ MA	
Other Requirements		
NCQA Elements		
References	1. ADCETRIS® (Brentuximab vedotin) for injection, for intravenous use [prescribing information]. Bothell, WA: Seattle Genetics, Inc.; Revised November 2018. Accessed February 2019. 2. The NCCN Drugs & Biologics Compendium® Brentuximab vedotin © 2018 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org/professionals/drug_compendium/content/. Accessed February 25,2019.	

Revision History

Revision Date	Revision Description	Revision Made By
10/01/2012	New CCC	Rachel Koh, RPh, MBA
10/12/2012	Approval	P&T Committee
10/11/2013	Approval	P&T Committee
11/07/2014	Approval	P&T Committee
10/23/2015	Revision review	Frances McGaugh, Pharm.D.
05/01/2017	All content updated	Sophia Yun, PharmD
05/21/2017	Approval	MMLT
02/14/2018	Updates revision	Catherine Vu, PharmD

03/01/2018	Approval	MMLT
03/09/2018	Reassigned from UM to Pharmacy	Cindy Bush
02/25/2019	Revision review	Jennifer Farley, PharmD
03/08/2019	Approval	UM Pharmacy Subcommittee