Clinical Policy Bulletin: Brentuximab (Adcetris)

Number: 0823

Policy

Note: REQUIRES PRECERTIFICATION*

Aetna considers brentuximab vedotin (Adcetris) medically necessary for the following indications:

- Salvage therapy for persons with classic Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least 2 prior multi-agent chemotherapeutic regimens
- Consolidation therapy following stem cell transplant in patients who have classical HL and are at a high risk of relapse or progression.
- Second-line or subsequent therapy for relapse of CD30+ AIDS-related diffuse large B-cell lymphoma, primary effusion lymphoma, and lymphoma associated with Castleman's disease in noncandidates for high-dose therapy
- Second-line or subsequent therapy for CD30+ relapsed or refractory diffuse large B-cell lymphoma in noncandidates for high-dose therapy
- First-line chemotherapy for mycosis fungoides/Sezary syndrome
- Second-line or subsequent therapy for relapsed or refractory systemic anaplastic large cell lymphoma (ALCL) (excluding cutaneous ALCL) and for CD30+ peripheral T-cell lymphoma (PTCL)
- Second-line or subsequent therapy for CD30+ relapsed or refractory primary cutaneous diffuse large B-cell lymphoma, leg type in noncandidates for high-dose therapy
- Single-agent therapy for primary cutaneous anaplastic large cell lymphoma (ALCL) with multifocal lesions or cutaneous ALCL with regional nodes (excludes systemic ALCL)
- Single-agent therapy for symptomatic lymphomatoid papulosis (LyP) or LyP with extensive lesions if refractory to all primary treatment options.

Continued use of brentuximab vedotin is considered not medically necessary for persons whose disease has progressed with brentuximab vedotin or who have developed intolerance to this drug.
Aetna considers brentuximab vedotin contraindicated and experimental and investigational for use in persons diagnosed with progressive multifocal leukoencephalopathy.

Aetna considers brentuximab vedotin experimental and investigational for all other indications (e.g., renal cell cancer, and small cell lung cancer because its effectiveness for indications other than the ones listed above has not been established.

**Note:** * Precertification of brentuximab vedotin is required of all Aetna participating providers and members in applicable plan designs. For precertification of brentuximab vedotin, call (866) 503-0857, or fax (866) 267-3277.

**Note:** A "Boxed Warning" highlighting the risk of progressive multifocal leukoencephalopathy was added to the drug label of brentuximab vedotin (Adcetris) in January 2012.

**Note:** Treatment with brentuximab should be continued until disease progression or unacceptable toxicity.

See also CPB 0494 - Hematopoietic Cell Transplantation for Non-Hodgkin's Lymphoma, CPB 0495 - Hematopoietic Cell Transplantation for Hodgkin's Disease, and CPB 0634 - Non-myeloablative Bone Marrow/Peripheral Stem Cell Transplantation (Mini-Allograft / Reduced Intensity Conditioning Transplant).

**Background**

Lymphomas are cancers of the lymphatic system. Hodgkin's lymphoma (HL) and anaplastic large-cell lymphoma (ALCL, a rare type of non-Hodgkin lymphoma) are the two most common tumors expressing CD30. The National Cancer Institute estimates that about 9,000 new cases of HL will be diagnosed in the United States in 2011 and about 1,300 people will die from the disease. CD30 is abundantly and selectively expressed on the surface of Hodgkin Reed-Sternberg cells, ALCLs, and other lymphoid malignancies as well as on several non-lymphoid malignancies including selected germ cell tumors. Expression of CD30 on normal cells is highly restricted, thereby allowing differential targeting of malignant cells. CD30, a member of the tumor necrosis factor (TNF)-receptor family has pleiotropic biologic functions, and antibodies targeting CD30 and other TNF family receptors can exhibit both agonistic and antagonistic signaling functions (Alley et al, 2010; Deutsch et al, 2011; NCI, 2011).

Patients with relapsed or refractory HL and ALCL usually have a poor prognosis. Individuals with these histologies who subsequently progress after salvage chemotherapy and autologous stem cell transplantation (ASCT) have very limited treatment options and are in need of novel effective therapies. Recently, the antibody-drug conjugate (ADC) field has made significant progress as a consequence of careful optimization of several parameters, including mAb specificity, drug potency, linker technology, as well as the
stoichiometry and placement of conjugated drugs. The underlying reason for this has been obtained in pre-clinical biodistribution and pharmacokinetics studies showing that targeted delivery leads to high intra-tumoral free drug concentrations, while non-target tissues are largely spared from chemotherapeutic exposure. Developments in the field have led to an increase in the number of ADCs being tested clinically. Recently, ADCs targeting CD30, such as brentuximab vedotin (cAC10-vcMMAE, SGN 35, SGN-35), have shown striking activity in phase I and II clinical studies, with manageable toxicity. This has defined an important emerging role for targeting of CD30 in the setting of HL, ALCL, and possibly other CD30+ malignancies. Brentuximab vedotin consists of 3 components: (i) the chimeric IgG antibody cAC10, specific for human CD30, (ii) the potent microtubule disruptive cytotoxic agent, mono-methyl auristatin E (MMAE), and (iii) a protease-cleavable linker that co-valently attaches MMAE to cAC10 (Ansell, 2011; Deutsch et al, 2011).

In a phase I, open-label, multi-center dose-escalation study, Younces et al (2010) administered brentuximab vedotin (at a dose of 0.1 to 3.6 mg/kg body weight) every 3 weeks to 45 patients with relapsed or refractory CD30-positive hematologic cancers, primarily HL and ALCL. Patients had received a median of 3 previous chemotherapy regimens (range of 1 to 7), and 73 % had undergone autologous stem-cell transplantation (ASCT). The maximum tolerated dose was 1.8 mg/kg, administered every 3 weeks. Objective responses, including 11 complete remissions, were observed in 17 patients. Of 12 patients who received the 1.8-mg/kg dose, 6 (50 %) had an objective response. The median duration of response was at least 9.7 months. Tumor regression was observed in 36 of 42 patients who could be evaluated (86 %). The most common adverse events were diarrhea, fatigue, nausea, neutropenia, pyrexia, and peripheral neuropathy. The authors concluded that brentuximab vedotin induced durable objective responses and resulted in tumor regression for most patients with relapsed or refractory CD30-positive lymphomas in this phase I study. Treatment was associated primarily with grade 1 or 2 (mild-to-moderate) toxic effects.

Foyil and Bartlett (2011) described the preliminary findings of brentuximab vedotin for the treatment of patients with CD30+ lymphomas in large phase II clinical trials -- response rates of 75 % in relapsed/refractory HL and 87 % in relapsed/refractory systemic ALCL were reported. Brentuximab vedotin is well-tolerated with manageable side effects including peripheral sensory neuropathy. This ADC is currently under investigation in numerous clinical trials, including in combination with front-line chemotherapy for high-risk HL and in a placebo-controlled, phase III trial for patients with HL at high risk for residual disease following ASCT. The impressive response rates and limited toxicity of brentuximab vedotin are very promising for relapsed/refractory patients with few treatment options. In addition, the possibilities for incorporation into front-line therapies for both HL and systemic ALCL are intriguing.

On August 19, 2011, the Food and Drug Administration (FDA), under its accelerated approval program where surrogate endpoints are acceptable, approved brentuximab vedotin (Adcetris) for the treatment of patients with HL whose disease has progressed after ASCT or after 2 prior chemotherapy treatments for those who are not candidates for ASCT. The FDA also approved brentuximab vedotin for the treatment of patients with ALCL whose disease has progressed after 1 prior chemotherapy treatment. Brentuximab vedotin is the first new FDA-approved drug for HL since 1977 and the first drug specifically indicated for the treatment of ALCL. The effectiveness of brentuximab vedotin in patients with HL was evaluated in a clinical study involving 102 patients. In the open-lavel, single-
arm, multi-center trial, patients were only treated with brentuximab vedotin. The study’s primary endpoint was objective response rate, the percentage of patients who experienced complete or partial cancer shrinkage or disappearance following treatment. A total of 73 % of patients achieved either a complete or partial response to the treatment. On average, these patients responded to the therapy for 6.7 months. The effectiveness of brentuximab vedotin in patients with systemic ALCL was evaluated in a single clinical study involving 58 patients. In the phase II, open-label, single-arm, multi-center trial, patients were only treated with brentuximab vedotin. Similar to the HL trial, the trial’s primary endpoint was objective response rate. Of the patients receiving brentuximab vedotin for ALCL, 86 % experienced either a complete or partial response and responded on average for 12.6 months. The most common adverse reactions experienced with brentuximab vedotin were anemia, cough, diarrhea, fatigue, fever, nausea, neutropenia, peripheral sensory neuropathy, thrombocytopenia, upper respiratory infection, and vomiting.

Oki and Younes (2012) noted that brentuximab vedotin has been approved by the FDA for the treatment of relapsed or refractory HL and ALCL. The effectiveness of brentuximab vedotin in other CD30(+) lymphomas is currently being investigated. These investigators reviewed the currently available treatment options for systemic peripheral T-cell lymphomas (PTCL) and the role of brentuximab vedotin in relapsed or refractory ALCL. In addition, ongoing clinical trial of brentuximab vedotin in relapsed PTCL and combination therapy with other chemotherapies for initial treatment of CD30(+) lymphoma were also reviewed. The authors concluded that brentuximab vedotin has established its role in the treatment of relapsed or refractory HL and ALCL. In the next few years, the effectiveness of this agent in other CD30(+) lymphomas will be described. The safety and effectiveness of several brentuximab-based combination regimens, including use as front-line chemotherapy is under investigation.

The recommended dosage of brentuximab vedotin (Adcetris) is 1.8 mg/kg body weight administered only as an intravenous infusion over 30 minutes every 3 weeks. Treatment can be continued until disease progression or unacceptable toxicity.

On January 13, 2012, the FDA notified the public that 2 additional cases of progressive multifocal leukoencephalopathy (PML) have been reported with Adcetris (brentuximab vedotin). Due to the serious nature of PML, a new Boxed Warning high-lighting this risk has been added to the drug label. At the time of Adcetris’ approval in August 2011, 1 case of PML was described in the Warnings and Precautions section of the label. In addition, a new Contraindication warning against use of Adcetris with bleomycin due to increased risk of pulmonary toxicity has been added to the drug label.

The National Comprehensive Cancer Network (NCCN)’s Drugs & Biologics Compendium (2015) lists the following indications for brentuximab vedotin (Adcetris):

Salvage therapy for persons with classic Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least 2 prior multi-agent chemotherapeutic regimens
Second-line or subsequent therapy for relapse of CD30+ AIDS-related diffuse large B-cell lymphoma, primary effusion lymphoma, and lymphoma associated with Castleman’s disease in noncandidates for high-dose therapy

Second-line or subsequent therapy for CD30+ relapsed or refractory diffuse large B-cell lymphoma in noncandidates for high-dose therapy

First-line chemotherapy for:

- stage IA-IIA mycosis fungoides with histologic evidence of folliculotrophic or large cell transformation or stage IIB with generalized extent tumor, transformed, and/or folliculotrophic disease with or without skin-directed therapy
- stage IV non-Sezary mycosis fungoides or visceral disease
- refractory or progressive stage III mycosis fungoides or Sezary Syndrome

Second-line therapy for relapsed or refractory systemic nodal anaplastic large cell lymphoma (ALCL) (excluding cutaneous ALCL)

Second-line therapy for CD30+ peripheral T-cell lymphoma (PTCL)

Second-line or subsequent therapy for CD30+ relapsed or refractory primary cutaneous diffuse large B-cell lymphoma, leg type in noncandidates for high-dose therapy

Single-agent therapy for primary cutaneous anaplastic large cell lymphoma (ALCL) with multifocal lesions or cutaneous ALCL with regional nodes (excludes systemic ALCL) as

- primary treatment
- therapy for relapsed or refractory disease

Single-agent therapy for symptomatic lymphomatoid papulosis (LyP) or LyP with extensive lesions if refractory to all primary treatment options.

Bhatt and colleagues (2013) stated that primary effusion lymphoma (PEL) is an aggressive subtype of non-Hodgkin lymphoma characterized by short survival with current therapies, emphasizing the urgent need to develop new therapeutic approaches. Brentuximab vedotin is an effective treatment of relapsed CD30-expressing HL and systemic ALCL. These researchers demonstrated that PEL cell lines and primary tumors express CD30 and thus may serve as potential targets for brentuximab vedotin therapy. In-vitro treatment with brentuximab vedotin decreased cell proliferation, induced cell cycle arrest, and triggered apoptosis of PEL cell lines. Furthermore, in-vivo brentuximab vedotin promoted tumor regression and prolonged survival of mice bearing previously reported UM-PEL-1 tumors as well as UM-PEL-3 tumors derived from a newly established and characterized Kaposi’s sarcoma-associated herpesvirus- and Epstein-Barr virus-positive PEL cell line. The authors concluded that these findings demonstrated for the first time that brentuximab vedotin may serve as an effective therapy for PEL and provide strong pre-clinical indications for evaluation of brentuximab vedotin in clinical studies of PEL patients.

The American College of Radiology’s “Appropriateness Criteria® pediatric Hodgkin lymphoma” (Terezakis et al, 2012) stated that “Newer drugs promise great efficacy with less toxicity. Targeted therapy with brentuximab vedotin, an antibody-drug conjugate that targets CD30, has shown excellent results in early clinical trials. Pediatric trials are...”
underway to assess its efficacy and toxicity, and discussions about incorporating it into large clinical trials are under way”.

Newland et al (2013) noted that HL and systemic ALCL (sALCL), which is a subtype of non-Hodgkin lymphoma (NHL), are relatively uncommon lympho-proliferative types of cancer. These malignancies are highly curable with initial treatment. Nonetheless, some patients are refractory to or relapse after first- and second-line therapies, and outcomes for these patients are less promising. Brentuximab vedotin is a CD30-directed antibody-cytotoxic drug conjugate that has demonstrated efficacy in response rates (objective response rates and complete response) when given to patients with refractory or relapsed HL and sALCL. Although not compared directly in clinical trials, the response rates with brentuximab vedotin are higher than those of several current treatments for refractory or relapsed HL and sALCL. Adverse effects associated with brentuximab vedotin are considered manageable. Nonetheless, several serious adverse effects (e.g., neutropenia, peripheral sensory neuropathy, tumor lysis syndrome, Stevens-Johnson syndrome, and progressive multifocal leukoencephalopathy, resulting in death) have been reported with its use. Despite a lack of survival and patient reported outcome data, the FDA granted accelerated approval to brentuximab vedotin for the treatment of HL after failure of ASCT or at least 2 combination chemotherapy regimens, and for sALCL after failure of at least 1 combination chemotherapy regimen. With this approval, brentuximab vedotin is the first FDA-approved agent for the treatment of HL in over 3 decades and the first agent specifically indicated to treat sALCL. Results of ongoing prospective trials should determine if brentuximab vedotin has a survival benefit when compared directly with standard treatment and if brentuximab vedotin is safe and effective when given earlier in the disease process, or when used with other chemotherapy for the treatment of HL and sALCL or other CD30-positive malignancies.

Forero-Torres et al (2012) stated that brentuximab vedotin induces durable objective responses in patients with relapsed or refractory HL after ASCT. The objective of this post-hoc analysis was to characterize the safety and effectiveness of brentuximab vedotin for patients with relapsed or refractory HL who refused or were ineligible for ASCT. This case series included 20 transplant-naïve patients who were enrolled in 2 phase I multi-center studies. Patients received brentuximab vedotin intravenously every 3 weeks or every week for 3 out of 4 weeks. The majority of patients were transplant-naïve because of chemo-refractory disease. Median age was 31.5 years (range of 12 to 87 years). Treatment-emergent adverse events in greater than 20% of patients were peripheral neuropathy, fatigue, nausea, pyrexia, diarrhea, weight decreased, anemia, back pain, decreased appetite, night sweats, and vomiting; most events were grade 1 or 2. Six patients obtained objective responses: 2 complete remissions and 4 partial remissions. Median duration of response was not met; censored durations ranged from greater than 6.8 to greater than 13.8 months; 3 of 6 responders subsequently received ASCT. The authors concluded that brentuximab vedotin was associated with manageable adverse events in transplant-naïve patients with relapsed or refractory HL. The objective responses observed demonstrated that anti-tumor activity is not limited to patients who received brentuximab vedotin after ASCT. They stated that the promising activity observed in this population warrants further study.

Hadley (2012) stated that "Brentuximab vedotin is being developed in a joint collaboration between Seattle Genetics and Millennium: The Takeda Oncology Company. In August 2011, it was approved by the FDA for the treatment of patients with HL and anaplastic large cell lymphoma (ALCL). Brentuximab vedotin is an antibody-drug conjugate that
specifically targets the TNF receptor superfamily member 8 (CD30) antigen on the surface of cancer cells to induce cell death. Brentuximab vedotin has shown efficacy in inducing apoptosis in HL and ALCL cell lines that express CD30 and reducing tumor size in preclinical models. Brentuximab vedotin is under clinical evaluation for the treatment of relapsed or refractory HL and ALCL in both adults and children. It is being investigated for use as a combination agent with pre-existing frontline chemotherapies and as a stand-alone salvage therapy for use prior to autologous stem cell transplant. Treatment with brentuximab vedotin is generally well-tolerated although it is associated with grade 1-2 adverse reactions such as neutropenia and there have been reports of grade 3-4 serious adverse events. In particular its use with chemotherapy regimens that include bleomycin is contraindicated because of adverse pulmonary effects”.

Isidori and colleagues (2013) noted that HL has been a fascinating challenge for physicians and investigators since its recognition during the 19th century. However, many questions still remain unanswered. One issue regards high-dose therapy followed by ASCT, which has yet to find its place among several guidelines. Other topics are still controversial with respect to transplantation for HL, including its role for newly diagnosed patients with advanced stage disease, the optimal timing of transplantation, the best conditioning regimen and the role of allogeneic/haplo-identical SCT. Moreover, the potential use of localized radiotherapy or immunologic methods to decrease post-transplant recurrence, the role of novel agents such as brentuximab vedotin and their positioning in the treatment algorithm of resistant/relapsed HL patients, either before transplant to boost salvage therapy or after transplant as consolidation/maintenance, are burning questions without an answer”.

Burris (2013) noted that with the recent approvals of brentuximab for the treatment of refractory HL and ado-trastuzumab emtansine for relapsed metastatic HER2+ breast cancer, the hope for delivering targeted chemotherapy in the form of an ADC against many cancers is rapidly growing. The strategy of delivering a potent cytotoxic via a monoclonal antibody to a tumor has been made feasible by marked advances in the technology of formulating and manufacturing these ADCs. The development of stable linkers together with the identification of relevant biomarkers has been a key to the success of this class of agent. The possibilities for deploying this technology in the treatment of a wide range of solid cancers are limited only by the discovery of suitable targets, those which are highly expressed on cancer cells and not, or minimally, on normal tissues. That said, with the improved linker engineering, the ADC affords the best opportunity at shrinking tumors while minimizing side effects. The authors stated that a variety of ADCs are in clinical trials studying a number of different tumor types as diverse as small cell lung and renal cell cancer.

UpToDate reviews on “Treatment of advanced stage (IIB to IV) mycosis fungoides” (Hoppe and Kim, 2014) and “Treatment of Sézary syndrome” (Kim and Rook, 2014) do not mention brentuximab as a therapeutic option. Also, per NCCN’s Drugs & Biologics Compendium (2014) doe not list mycosis fungoides, primary effusion lymphoma, Sezary syndrome as well as use prior to autologous stem cell transplantation as recommended indications of brentuximab (Adcetris).
Other CPT codes related to the CPB:

38204  Management of recipient hematopoietic progenitor cell donor search and cell acquisition

38205  Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogenic

38206  autologous

38230  Bone marrow harvesting for transplantation

38232  autologous

38240  Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor

38241  autologous transplantation

77261-77295  Radiation therapy

96401-96450  Chemotherapy administration code range

HCPCS codes covered if selection criteria are met:

J9042  Injection, brentuximab vedotin, 1 mg

Other HCPCS codes related to the CPB:

J9000 - J9999  Chemotherapy drugs code range

Q0083 - Q0085  Chemotherapy administration

S2150  Bone marrow or blood-derived peripheral stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including; pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition

ICD-9 codes covered if selection criteria are met:

200.60 - 200.68  Anaplastic large cell lymphoma [after failure of at least 1 prior multi-agent chemotherapeutic regimen] [not covered for cutaneous anaplastic large cell lymphoma (ALCL)]

201.00 - 201.98  Hodgkin's disease [after failure of autologous stem cell transplant (ASCT) or after failure of at least 2 prior multi-agent chemotherapeutic regimens in persons who are not ASCT candidates][not covered as monotherapy for first-line treatment]

202.70 - 202.78  Peripheral t-cell lymphoma [only covered as a second-line therapy for CD30+ peripheral T-cell lymphoma]
ICD-9 codes not covered for indications listed in the CPB (not an all-inclusive list):

046.3  Progressive multifocal leukoencephalopathy (PML)

162.2 - 162.9  Malignant neoplasm of bronchus and lung [small cell lung cancer]

189.0 - 189.1  Malignant neoplasm of kidney and other and unspecified urinary organs [renal cell cancer]

200.00 - 200.58, 200.70 - 200.88  Lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue

202.00 - 202.68  Other malignant neoplasms of lymphoid and histiocytic tissue [includes Mycosis fungoides and Sezary syndrome]

202.80 - 202.88  Other malignant lymphomas [non-Hodgkin’s]

202.90 - 202.98  Other and unspecified malignant neoplasms of lymphoid and histiocytic tissue

238.79  Other lymphatic and hematopoietic tissues [CD30-positive lymphoproliferative disorders]

Other ICD-9 codes related to the CPB:

995.27  Other drug allergy [intolerance to brentuximab vedotin]

V58.11 - V58.12  Encounter for antineoplastic chemotherapy and immunotherapy

E933.1  Adverse effect of antineoplastic and immunosuppressive drugs [intolerance to brentuximab vedotin]

The above policy is based on the following references:


6. U.S. Food and Drug Administration (FDA). FDA approves Adcetris to treat two types of lymphoma. Press Release. Silver Spring, MD: FDA; August 19, 2011. Available at:


18. Hoppe RT, Kim YH. Treatment of advanced stage (IIIB to IV) mycosis fungoides. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed May 2014.

