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MEDICAL POLICY – 2.03.502

Monoclonal Antibodies for the Treatment of Lymphoma

BCBSA Ref. Policy:	2.03.05
Effective Date:	Aug. 1, 2018
Last Revised:	July 10, 2018
Replaces:	N/A

RELATED MEDICAL POLICIES:

5.01.549	Off-Label Use of Drugs and Biologic Agents
5.01.550	Pharmacotherapy of Arthropathies
5.01.556	Rituximab: Non-oncologic and Miscellaneous Uses
8.01.533	Radioimmunotherapy in the Treatment of Non-Hodgkin Lymphoma

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POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

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Introduction

An antibody is a blood protein. When the immune system detects an unhealthy cell, antibodies attach themselves a molecule known as an antigen on that unhealthy cell. The antibody then acts as flag for other immune system cells, causing those other immune system cells to swarm to the area and fight the unhealthy cell. Cancer cells can evade the immune system by reproducing very quickly, avoiding detection, or completely blocking the immune system. Monoclonal antibodies are drugs that work with the body's natural immune response. Monoclonal antibodies are produced in a laboratory and made to specifically attach to the antigens which are typically found in high numbers on cancer cells. This policy describes when treatment with monoclonal antibodies may be approved to treat lymphoma.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Rituxan® (rituximab)	**Rituxan® (rituximab) is a CD20-directed cytolytic antibody and may be considered medically necessary (for the following labeled indications) in the treatment of patients with:** • Non-Hodgkin's Lymphoma (NHL) and • Chronic Lymphocytic Leukemia (CLL) **Rituxan® (rituximab) may be considered medically necessary for the following off-label indications:** • Treatment of any B-cell or other Lymphoid malignancies with documented CD20 antigen expression (eg, ALL, CLL/SLL, primary CNS lymphomas, AIDS-related B-cell lymphoma, follicular lymphoma, hairy cell leukemia, lymphoblastic lymphoma, MALT lymphoma, Hodgkin's lymphoma, Burkitt's lymphoma, mantle cell lymphoma, splenic marginal zone lymphoma, multiple myeloma and Waldenstrom's macroglobulinemia and CD-20 positive leptomenigeal metastases) • Treatment of posttransplant lymphoproliferative disorder • First-line therapy of monomorphic or polymorphic post-transplant lymphoproliferative disorder (PTLD) • Second-line therapy for persistent or progressive PTLD • Maintenance therapy for polymorphic PTLD

Drug	Medical Necessity

Rituxan Hycela™ (rituximab and hyaluronidase human)	**Rituxan Hycela™ (rituximab and hyaluronidase human) is a CD20-directed cytolytic antibody and hyaluronidase human, an endoglycoside, and may be considered medically necessary (for the following labeled indications) in the treatment of adult patients with:**
	• Follicular Lymphoma (FL)
	  ○ Used as a single agent for relapsed or refractory FL
	  ○ Used in combination with first-line chemotherapy for previously untreated FL
	  ○ Used as single agent maintenance therapy in patients achieving a complete or partial response to rituximab in combination with chemotherapy
	  ○ Used as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy for non-progressing (including stable disease)
	• Diffuse Large B-cell Lymphoma (DLBCL)
	  ○ In combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens for previously untreated diffuse large B-cell lymphoma
	• Chronic Lymphocytic Leukemia (CLL)
	  ○ In combination with fludarabine and cyclophosphamide (FC) for previously untreated and previously treated CLL
	
	Rituxan Hycela™ (rituximab and hyaluronidase human) may be considered medically necessary for any other labeled or off-label indications of Rituxan®.
	
	Note: Initiate treatment with Rituxan Hycela only after patients have received at least ONE FULL DOSE of a rituximab product by intravenous infusion.

Arzerra® (ofatumumab)	**Arzerra® (ofatumumab) may be considered medically necessary for the following labeled indications:** • Treatment in combination with chlorambucil for the treatment of previously untreated patients with chronic lymphocytic leukemia (CLL) for whom fludarabine-based therapy is considered inappropriate

Drug	Medical Necessity
	• Treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab.
Adcetris® (brentuximab vedotin)	**Adcetris® (brentuximab vedotin) may be considered medically necessary for the following labeled indications:** • Previously untreated Stage III or IV classical Hodgkin lymphoma (cHL), in combination with chemotherapy. • Classical Hodgkin lymphoma at high risk of relapse or progression as post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation. • Classical Hodgkin lymphoma after failure of auto-HSCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates. • Systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen. • Primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30expressing mycosis fungoides (MF) who have received prior systemic therapy. •

Drug	Investigational
Rituxan® (rituximab)	**Rituxan® (rituximab) is considered investigational for the following off-label indication:** • Treatment of lymphoid B-cell malignancies that do not express CD20 antigen

Coding

Code	Description
HCPCS	
J9042	Injection, brentuximab vedotin (Adcetris®), 1 mg
J9302	Injection, ofatumumab (Arzerra®), 10 mg
J9310	Injection, rituximab (Rituxan®), 100 mg

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)

Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is classified as an indolent non-Hodgkin's lymphoma (NHL). When CLL/SLL is relapsed or refractory and CD20+ B-cells (not T-cells) are present, treatment is appropriate with Rituximab.

Rituxan® and Arzerra® are intended for IV infusion administration.

Benefit Application

State or federal mandates regarding off-label uses of drugs approved by the U.S. Food and Drug Administration (FDA) may supersede this policy.

Evidence Review

Description

Normal and malignant hematopoietic cells express various antigens on their surfaces, including: CD20 expressed by B-lymphocytes and B-cell malignancies; CD33, present on myeloid progenitors and acute myeloid leukemia (AML); and CD52, expressed by normal and malignant T- and B-lymphocytes. Monoclonal antibodies have been developed to each of the above antigens and have been investigated for the following labeled and off-label uses.

Rituxan® (rituximab) is a CD20-directed cytolytic antibody indicated for the treatment of patients with following labeled indications:

- Non-Hodgkin's Lymphoma (NHL), and
- Chronic Lymphocytic Leukemia (CLL)

Rituximab and hyaluronidase human (Rituxan Hycela™) is a CD20-directed cytolytic antibody and hyaluronidase human, indicated for the treatment of adult patients with the following labeled indications:

- Follicular Lymphoma (FL)
- Diffuse Large B-cell Lymphoma (DLBCL)
- Chronic Lymphocytic Leukemia (CLL)

Arzerra® (ofatumumab): human monoclonal antibody to the CD20 antigen. Labeled indications:

- Treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab.

Brentuximab vedotin is an ADC. 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).

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.

NCCN Compendium

The National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium is based directly on the NCCN Clinical Practice Guidelines in Oncology. The compendium lists specific panel recommendations for off-label uses of drugs, and each recommendation is supported by a level of evidence category.

The NCCN Categories of Evidence and Consensus used in the recommendations are:

- Category 1: The recommendation is based on high level evidence (eg, randomized controlled trials) and there is uniform NCCN consensus.

- Category 2A: The recommendation is based on lower level evidence and there is uniform NCCN consensus.
- Category 2B: The recommendation is based on lower level evidence and there is nonuniform NCCN consensus (but no major disagreement).
- Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

In June 2008, the NCCN Compendium became one of four references for the Centers for Medicare & Medicaid Services (CMS) for oncology coverage policy.

In its national coverage decision, CMS states that, in general, a use identified by the NCCN Compendium is medically accepted if the indication is a Category 1 or 2A as defined by NCCN. A use is not medically accepted if the indication is a category 3 in NCCN.

The local CMS contractor, Noridian Administrative Services (NAS), has issued an additional coverage statement regarding Category 2B:

> NAS recognizes NCCN Categories of Evidence Levels Category 1 and Category 2A ONLY as medically accepted indications. If a provider chooses to use NCCN level 2B in support of a chemotherapeutic drug used off-label in an anti-cancer chemotherapeutic regimen, NAS expects that the provider will make available to NAS significant peer-reviewed Phase II or Phase III studies demonstrating such support. In the absence of such studies, level 2B evidence does not support such use.

The following policy considers only the off-label indications for rituximab and atumumab.

Background

Rituxan® (rituximab)

Regarding Rituxan® (rituximab) for patients with intermediate or aggressive non-Hodgkin's lymphoma (NHL), an interim analysis of a randomized controlled trial is available in abstract form. The trial compared rituximab plus combination chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone, aka CHOP) to CHOP therapy alone in 400 patients with previously treated diffuse large B-cell lymphoma. By intent–to-treat analysis, event-free and overall survival at 12 months was superior in the rituximab plus CHOP arm. In 2002, final results of this trial were published by Coiffier et al., confirming the superior outcomes in the combination arm. In the Coiffier study, event-free survival at 2 years (CI 95%) was 57% in the

CHOP + Rituximab arm and 38% in the CHOP alone arm. A 2002 TEC Assessment also found Rituximab met criteria for treatment of patients with intermediate or aggressive B-cell non-Hodgkin's lymphoma based on the Coiffier study.

In a randomized, Phase III trial of 122 patients with untreated advanced-stage mantle cell lymphoma, Lenz and colleagues reported patients receiving cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) plus rituximab (n=62) had significantly superior outcomes than patients receiving CHOP alone (n=60). Complete response rates and median time to treatment failure in the CHOP plus rituximab group vs the CHOP alone group were 34% vs. 7% (p=0.00024) and 21 months versus 14 months (p=0.0131), respectively. Toxicities were reported to be acceptable and similar in both treatment groups.

The indications for off-label use of rituximab were determined by:

- Considering the limited but evolving evidence in clinical trials indicating that CD20 expression enhanced susceptibility to this drug, and thus a response was more likely;
- Soliciting the expert opinion of physician specialists on its accepted use; and
- National Comprehensive Cancer Network Clinical Practice Guidelines for Non-Hodgkin's Lymphomas.

Rituxan Hycela™ (rituximab and hyaluronidase human)

Evidence for efficacy and safety of Rituxan Hycela™ (rituximab and hyaluronidase human) was evaluated in three studies of each specified indication. All studies demonstrated comparability of the subcutaneous (SC) formulation to the intravenous (IV) formulation of rituximab.

Follicular Lymphoma

The SABRINA study was a randomized, controlled, open-label, multicenter Phase 3 trial that evaluated 410 patients with previously untreated CD20-positive FL of Grade 1, 2, or 3a who received either IV Rituxan® (rituximab) or one cycle of an IV rituximab product followed by SC Rituxan Hyclea™ (rituximab), plus chemotherapy. The primary endpoint was overall response (complete response, unconfirmed complete response, and partial response) at the end of induction, which amounted to 84.9% (95% CI 79.2 – 89.5) in the IV group and 84.4% (95% CI 78.7 – 89.1) in the SC group, for a differenceof -0.5% (95% CI -7.7 – 6.8). The frequency of adverse events was similar in both groups (95% in the IV group and 96% in the SC group).

Diffuse Large B-Cell Lymphoma

The MabEase study was a randomized, controlled, open-label, multicenter Phase 3b trial that evaluated 576 patients with previously untreated CD20-positive DLBCL who received either IV rituximab or one cycle of an IV rituximab product followed by SC rituximab, plus chemotherapy. The primary endpoint was complete response/unconfirmed complete response (CR/Cru) at the end of induction, which amounted to 50.6% (95% CI 45.3% - 55.9%) in the SC group and 42.4% (95% CI 35.1% - 49.7%) in the IV group (P=0.076). Safety profiles were similar between arms, with no unexpected safety signals.

Chronic Lymphocytic Leukemia

The SAWYER study was a randomized, controlled, open-label, multicenter, non-inferiority Phase 1b trial that evaluated 176 patients with previously untreated CD20-positive CLL who received either IV rituximab or one cycle of an IV rituximab product followed by SC rituximab, plus chemotherapy. Overall, the study demonstrated non-inferiority of SC rituximab to IV rituximab through the primary endpoint of pharmacokinetic profiles. The geometric mean trough serum concentration was 97.5 mcg/mL in the SC group and 61.5 mcg/mL in the IV group, with an adjusted geometric mean ratio of 1.53 (90% CI 1.27 – 1.85). The proportion of patients reporting adverse events was similar between treatment arms.

Arzerra® (ofatumumab)

The evidence for efficacy and safety of Arzerra® (ofatumumab) is currently limited to uncontrolled clinical studies. This evidence suggests ofatumumab is efficacious for achieving an objective response in approximately 50% patients with fludrabine- or alemtuzumab-refractory CLL.

The drug also appears to have efficacy in some patients with rituximab-refractory disease.

Controlled clinical trials are needed to establish the superiority of ofatumumab over other therapeutic alternative (eg, rituximab). In addition, improved survival remains to be established.

Adcetris® (brentuximab vedotin)

The efficacy of Adcetris® (brentuximab vedotin) in patients with classical HL who relapsed after autologous hematopoietic stem cell transplantation was evaluated in one open-label, single-arm, multicenter trial. One hundred two patients were treated with 1.8 mg/kg of ADCETRIS intravenously over 30 minutes every 3 weeks. An independent review facility (IRF) performed efficacy evaluations which included overall response rate (ORR = complete remission [CR] + partial remission [PR]) and duration of response as defined by clinical and radiographic measures including computed tomography (CT) and positron-emission tomography (PET) as defined in the 2007 Revised Response Criteria for Malignant Lymphoma (modified). The 102 patients ranged in age from 15–77 years (median, 31 years) and most were female (53%) and white (87%). Patients had received a median of 5 prior therapies including autologous hematopoietic stem cell transplantation. Duration of response is calculated from date of first response to date of progression or data cutoff date.

Ongoing and Unpublished Clinical Trials

Randomized Placebo-controlled Clinical Trial in Classical HL Post-auto-HSCT Consolidation (Study 3)

The efficacy of Adcetris® (brentuximab vedotin) in patients with classical HL at high risk of relapse or disease progression post-auto-HSCT was studied in a randomized, double-blind, placebo-controlled clinical trial. Three hundred twenty-nine patients were randomized 1:1 to receive placebo or Adcetris® (brentuximab vedotin) 1.8 mg/kg intravenously over 30 minutes every 3 weeks for up to 16 cycles, beginning 30–45 days post-auto-HSCT. Patients in the placebo arm with progressive disease per investigator could receive Adcetris® (brentuximab vedotin) as part of a separate trial. The primary endpoint was progression-free survival (PFS) determined by IRF. Standard international guidelines were followed for infection prophylaxis for HSV, VZV, and PCP post-auto-HSCT [see Clinical Trial Experience (6.1)].

High risk of post-auto-HSCT relapse or progression was defined according to status following frontline therapy: refractory, relapse within 12 months, or relapse ≥12 months with extranodal disease. Patients were required to have obtained a CR, PR, or stable disease (SD) to most recent pre-auto-HSCT salvage therapy.

A total of 329 patients were enrolled and randomized (165 Adcetris® (brentuximab vedotin), 164 placebo); 327 patients received study treatment. Patient demographics and baseline characteristics were generally balanced between treatment arms. The 329 patients ranged in age

from 18–76 years (median, 32 years) and most were male (53%) and white (94%). Patients had received a median of 2 prior systemic therapies (range, 2–8) excluding autologous hematopoietic stem cell transplantation. PFS is calculated from randomization to date of disease progression or death (due to any cause). The median PFS follow-up time from randomization was 22 months (range, 0–49). Study 3 demonstrated a statistically significant improvement in IRF-assessed PFS and increase in median PFS in the Adcetris® (brentuximab vedotin) arm compared with the placebo arm. At the time of the PFS analysis, an interim overall survival analysis demonstrated no difference.

Clinical Trial in Relapsed sALCL (Study 2)

The efficacy of Adcetris® (brentuximab vedotin) in patients with relapsed sALCL was evaluated in one open-label, single-arm, multicenter trial. This trial included patients who had sALCL that was relapsed after prior therapy. Fifty-eight patients were treated with 1.8 mg/kg of ADCETRIS administered intravenously over 30 minutes every 3 weeks. An IRF performed efficacy evaluations which included overall response rate (ORR = complete remission [CR] + partial remission [PR]) and duration of response as defined by clinical and radiographic measures including computed tomography (CT) and positron-emission tomography (PET) as defined in the 2007 Revised Response Criteria for Malignant Lymphoma (modified).

The 58 patients ranged in age from 14–76 years (median, 52 years) and most were male (57%) and white (83%). Patients had received a median of 2 prior therapies; 26% of patients had received prior autologous hematopoietic stem cell transplantation. Fifty percent (50%) of patients were relapsed and 50% of patients were refractory to their most recent prior therapy. Seventy-two percent (72%) were anaplastic lymphoma kinase (ALK)-negative.

Duration of response is calculated from date of first response to date of progression or data cutoff date.

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

2004 Update

The U.S. Pharmacopoeial Convention (2003) has concluded that Rituxan® (rituximab) is accepted for the following off-label indications: a) as first-line treatment of diffuse aggressive

NHL; b) treatment of relapsed or refractory diffuse aggressive NHL; c) first-line treatment of intermediate to high-grade NHL; and d) first-line treatment of low-grade NHL.

2006 Update

Studies continue, but have not yet been published, which would indicate the safety and efficacy of Mylotarg® as a single-agent treatment for patients who are CD33-positive with AML in first relapse. Outcomes of these studies are awaited.

2008 Update

NCCN guidelines v.3.2008 recommends rituximab (preferred), or alkylating agents such as cyclophosphamide or chlorambucil as single agents for first-line therapy for follicular lymphoma in elderly or infirm patients.

2009 Update

Both R-CHOP (rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone) and R-CVP (rituximab with cyclophosphamide, vincristine and prednisone) have been used successfully in the treatment of patients with symptomatic follicular lymphoma (FL). Ganguly and Patel (2009 conducted a meta-analysis of relevant literature comparing both treatment arms for FL with response being the final endpoint. Two analyses were conducted: The first analysis compared R-CHOP to R-CVP as frontline agents for the treatment of FL and the second analysis included both untreated and relapsed patients. The authors report that for both studies, R-CVP was superior to R-CHOP when evaluating for complete response (CR). However for overall response (CR+PR), R-CHOP was superior. The authors concluded that both R-CHOP and R-CVP protocols achieve excellent overall response. In patients with known cardiac history, omission of anthracyclines is reasonable and R-CVP provides a competitive CR rate. In younger patients with FL where cumulative cardio-toxicity may be of importance in the long term and in whom future stem cell transplantation is an option, again R-CVP may be a more appealing option.

The Company recognizes uses of rituximab, ofatumumab, , and alemtuzumab listed in the NCCN Drugs and Biologics Compendium with Categories of Evidence and Consensus of 1 and 2A as proven and Categories of Evidence and Consensus of 2B and 3 as unproven. However, Category

2B uses may be considered for coverage if they are substantiated by provider submission of significant peer-reviewed Phase II or Phase III studies demonstrating treatment effectiveness.

2010 Update

Updated to reflect current NCCN Compendium recommendations as of February 2010. Added newly marketed anti-CD20 monoclonal antibody, ofatumumab. Added information concerning the voluntary withdrawal of gemtuzumab from the market.

2011 Update

Policy updated with literature review. Policy statements for Mylotarg® and supporting data removed from policy statement and any reference throughout the policy subsequent to FDA withdrawal of approval for this drug.

2012 Update

Policy updated to include NCCN recommendation for treatment of leptomeningeal metastases. (Category 2A) These may occur with various solid tumors, breast and lung being the most common. Therapy is palliative and usually of limited duration, as the average life expectancy of these patients is only a few weeks.

2013 Update

Policy updated to include NCCN recommendation for addition of rituximab in induction/consolidation treatment of, ALL, CLL/SLL, primary CNS lymphomas, AIDS-related B-cell lymphoma, follicular lymphoma, hairy cell leukemia, and lymphoblastic lymphoma. (Category 2A and above) Also treatment of post-transplant lymphoproliferative disorder. (Category 2A)

Added Arzerra® (ofatumumab) NCCN recommended off-label use for Waldenstrom's macroglobulinemia. (Category 2A)

Campath (alemtuzumab) removed from policy as it is no longer commercially available.

2014 Update

Policy updated to include new labeled indication in combination with chlorambucil for the treatment of previously untreated patients with chronic lymphocytic leukemia (CLL) for whom fludarabine-based therapy is considered inappropriate.

2015 Update

Policy updated with primary literature review and reference to NCCN guidelines. No new evidence was found that would require a change in this policy.

2016 Update

Policy updated with primary literature review and reference to NCCN guidelines. Adcetris criteria, description, and rationale were added to the policy.

2017 Update

Policy updated with primary literature review and reference to NCCN guidelines. Rituxan Hyclea™ criteria, description, and rationale were added to the policy.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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History

Date	Comments
08/15/01	Add to Medicine Section - New Policy
08/13/02	Replace Policy - Policy revised; policy statement changed regarding Rituximab for intermediate or aggressive NHL.
07/13/04	Replace Policy - Policy revised with literature updated; added the 2004 US Pharmacopeia and the American Hospital Formulary Service off-label indications to the Benefit Application section; clarification made: mantle cell was removed from investigational status; otherwise, policy statement unchanged.
12/14/04	Replace Policy / New Policy - Policy replaces BC.2.03.05 per direction from OAP 10/29/04 meeting. Indications changed from investigational to medically necessary.
10/11/05	Replace Policy - Scheduled reviewed. Added two off-label indications to Rituximab in policy statement.
02/06/06	Codes updated - No other changes.
06/23/06	Update Scope and Disclaimer - No other changes.
12/12/06	Replace Policy - Policy reviewed by P&T Committee on September 26, 2006; policy statement expanded to include the use of Alemtuzumab (CamPath®) in the treatment of malignancies other than CLL that express CD-52 antigen as a medically necessary indication; and the use of Gemtuzumab ozogamicin (Mylotarg®) in the treatment of malignancies other than CLL which express CD-33 antigen as a medically necessary indication; malignancies other than CD33-positive remain investigational, but the condition of AML has been removed from this particular statement indication.
02/22/07	Update References - Policy reviewed and recommended by OAP February 22, 2007. No change to policy statement.
04/10/07	Replace Policy - Policy Guidelines amended to indicate that Mylotarg is intended for IV administration.
06/10/08	Replace Policy - Policy updated with literature search. Policy statement under Rituxan updated to include: "Therapy of other B-cell malignancies that express CD-20 antigen including some cases of CD-20 positive Hodgkin's Disease and Monotherapy as first-line follicular lymphoma treatment for elderly patients, or others who are not good candidates for cytotoxic chemotherapy" as a medically necessary indication. Policy reviewed and recommended by OAP May 22, 2008. P&T reviewed and approved on May 27, 2008.

Date	Comments
02/10/09	Code Update - Code 273.3 added; no other changes.
05/12/09	Replace Policy - Policy statements revised to clarify off-label uses. Intent of policy remains unchanged. NCCN categories of evidence added to Description and Rationale. References added.
10/13/09	Cross Reference Update - No other changes.
05/11/10	Cross Reference Update - No other changes.
08/10/10	Replace Policy - Policy updated the Rituximab labeled indications reflecting the latest revision (02/2010) by deleting all the references to the other chemotherapy agents.Reviewed and recommended by P&T in March 2010; by OAP in May 2010. Mylotarg removed. Arzerra added.
10/19/11	Related Policy 5.01.01 added.
09/11/12	Replace policy. Policy updated with literature review. CD20 positive leptomenigeal metastases added to the list of approved off-label indications for rituximab.
11/26/12	Related Policies Update, add 5.01.526.
10/14/13	Replace policy. Within the Policy section, additional examples of off-label indications for Rituxan® have been added to the list of those considered medically necessary; Azerra® has an added medically necessary indication for salvage treatment of Waldenstrom's Macroglobulinemia / Lymphoplasmacytic lymphoma in rituximab-intolerant patients; and Campath® has been removed from the policy as it is no longer commercially available. Description, Policy Guidelines and Rationale sections updated in support of the changes within the Policy section. HCPCS code J9010 for Campath removed from the coding section.
11/20/13	Update Related Policies. 5.01.01 deleted and replaced with 5.01.549.
12/18/13	Update Related Policies. Change title to 5.01.526.
03/17/14	Update Related Policies. Add new policy 5.01.550 which replaces 5.01.526 and 5.01.601; they are now deleted.
08/11/14	Annual Review. Policy updated to include new labeled indication in combination with chlorambucil for the treatment of previously untreated patients with chronic lymphocytic leukemia (CLL) for whom fludarabine-based therapy is considered inappropriate. ICD-9 diagnosis codes removed.
11/05/14	Minor correction. Correct usage to "CD20" throughout the policy to be consistent. No other changes.
01/23/15	Update Related Policies. Add 5.01.556.
10/13/15	Annual Review. Policy updated with literature review; no change in policy statements. Remove CPT codes 96409-96417; these are not primarily utilized in adjudication.
01/01/17	Annual Review, approved December 13, 2016. Adcetris® criteria, description, and rationale were added to the policy.

Date	Comments
01/13/17	Coding update, added HCPCS code J9042.
12/01/17	Annual Review, approved November 14, 2017. Rituxan Hyclea™ criteria, description, and rationale were added to the policy.
07/01/18	Interim Review, approved June 5, 2018. Criteria for Rituxan revised for clarity. Removed HCPCS code J9999.
08/01/18	Interim Review, approved July 10, 2018. Updated Adcetris indications.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
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Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

አማሪኛ (Amharic):
ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ Premera Blue Cross ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀኖች ሊኖሩ ይችላሉ። የጤናን ሽፋንዎን ለመጠበቅና በእከፋፈል እርዳታ ለማግኘት በተውሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎት ይሆናል። ይህን መረጃ እንዲያገኙ እና ያለምንም ክፍያ በቋንቋዎ እርዳታ እንዲያገኙ መብት አለዎት።በስልክ ቁጥር 800-722-1471 (TTY: 800-842-5357) ይደውሉ።

العربية (Arabic):
يحوي هذا الإشعار معلومات هامة. قد يحوي هذا الإشعار معلومات مهمة بخصوص طلبك أو التغطية التي تريد الحصول عليها من خلال Premera Blue Cross. قد تكون هناك تواريخ مهمة في هذا الإشعار. وقد تحتاج لاتخاذ إجراء في تواريخ معينة للحفاظ على تغطيتك الصحية أو للمساعدة في دفع التكاليف. يحق لك الحصول على هذه المعلومات والمساعدة بلغتك دون تكبد أية تكلفة. اتصل بـ800-722-1471 (TTY: 800-842-5357)

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

Oromoo (Cushite):
Beeksisni kun odeeffannoo barbaachisaa qaba. Beeksisti kun sagantaa yookan karaa Premera Blue Cross tiin tajaajila keessan ilaalchisee odeeffannoo barbaachisaa qabaachuu danda'a. Guyyaawwan murteessaa ta'an beeksisa kana keessatti ilaalaa. Tarii kaffaltiidhaan deeggaramuuf yookan tajaajila fayyaa keessaniif guyyaa dhumaa irratti wanti raawwattan jiraachuu danda'a. Kaffaltii irraa bilisa haala ta'een afaan keessaniin odeeffannoo argachuu fi deeggarsa argachuuf mirga ni qabaattu. Lakkoofsa bilbilaa 800-722-1471 (TTY: 800-842-5357) tii bilbilaa.

Français (French):
Cet avis a d'importantes informations. Cet avis peut avoir d'importantes informations sur votre demande ou la couverture par l'intermédiaire de Premera Blue Cross. Le présent avis peut contenir des dates clés. Vous devrez peut-être prendre des mesures par certains délais pour maintenir votre couverture de santé ou d'aide avec les coûts. Vous avez le droit d'obtenir cette information et de l'aide dans votre langue à aucun coût. Appelez le 800-722-1471 (TTY: 800-842-5357).

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Enpòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kèk aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resevwa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rele nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):
Diese Benachrichtigung enthält wichtige Informationen. Diese Benachrichtigung enthält unter Umständen wichtige Informationen bezüglich Ihres Antrags auf Krankenversicherungsschutz durch Premera Blue Cross. Suchen Sie nach eventuellen wichtigen Terminen in dieser Benachrichtigung. Sie könnten bis zu bestimmten Stichtagen handeln müssen, um Ihren Krankenversicherungsschutz oder Hilfe mit den Kosten zu behalten. Sie haben das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Rufen Sie an unter 800-722-1471 (TTY: 800-842-5357).

Hmoob (Hmong):
Tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb. Tej zaum tsab ntawv tshaj xo no muaj cov ntsiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam los ntawm Premera Blue Cross. Tej zaum muaj cov hnub tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas peb kom koj ua tsis pub dhau cov caij nyoog uas teev tseg rau hauv daim ntawv no mas koj thiaj yuav tau txais kev pab cuam kho mob los yog kev pab them tej nqi kho mob ntawd. Koj muaj cai kom lawv muab cov ntshiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

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한국어 (Korean):
본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross 를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 본 통지서에는 핵심이 되는 날짜들이 있을 수 있습니다. 귀하는 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하는 이러한 정보와 도움을 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357) 로 전화하십시오.

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ភាសាខ្មែរ (Khmer):
សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរ៉ាប់រងរបស់អ្នកតាមរយៈ Premera Blue Cross ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ចេញសមត្ថភាព ដល់កំណត់ថ្ងៃជាក់ច្បាស់នានា ដើម្បីនឹងរក្សាទុកការជានាវ៉ាប់រងសុខភាពរបស់អ្នក ឬប្រាក់ជំនួយចេញផ្លែ។ អ្នកមានសិទ្ធិទទួលព័ត៌មាននេះ និងជំនួយនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-722-1471 (TTY: 800-842-5357)។

ਪੰਜਾਬੀ (Punjabi):
ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ Premera Blue Cross ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ . ਇਸ ਨੋਜਿਸ ਜਵਚ ਖਾਸ ਤਾਰੀਖਾ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀ ਜਸਹਤ ਕਵਰੇਜ ਰਿੱਖਣੀ ਹੋਵੇ ਜਾ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਛੁੱਕ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ਼ ਤੋਂ ਪਹਿਲਾਂ ਕੁੱਝ ਖਾਸ ਕਦਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫ਼ਤ ਵਿੱਚ ਤੇ ਆਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-722-1471 (TTY: 800-842-5357).

فارسی (Farsi):
این اعلامیه حاوی اطلاعات مهم میباشد .این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق Premera Blue Cross باشد. به تاریخ های مهم در این اعلامیه توجه نمایید .شما ممکن است برای حفظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کارهای خاصی احتیاج داشته باشید .شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-722-1471 (کاربران TTY تماس باشماره 800-842-5357) تماس برقرار نمایید.

Polskie (Polish):
To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócic uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):
Prezenta notificare conține informații importante. Această notificare poate conține informații importante privind cererea sau acoperirea asigurării dumneavoastre de sănătate prin Premera Blue Cross. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistența privitoare la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-722-1471 (TTY: 800-842-5357).

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Fa'asamoa (Samoan):
Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, Premera Blue Cross, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilo fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'amatalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):
Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay maaaring naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

ไทย (Thai):
ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับการการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือนี้ในภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 800-722-1471 (TTY: 800-842-5357)

Український (Ukrainian):
Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):
Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình Premera Blue Cross. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-722-1471 (TTY: 800-842-5357).