Monoclonal Antibodies for the Treatment of Lymphoma

Number 2.03.502
Effective Date January 1, 2017
Revision Date(s) 01/13/17; 12/13/16; 10/13/15; 08/11/14; 10/14/13; 09/11/12; 07/12/11; 08/10/10; 05/12/09; 06/10/08; 04/10/07; 12/12/06; 10/11/05; 12/14/04
Replaces 2.03.05

Rituxan®
Rituximab (Rituxan®) 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).

Rituximab (Rituxan®) may be considered medically necessary for the following off-label indications:

- Treatment of any B-cell or other Lymphoid malignancies that express CD20 antigen, including but not limited to, 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 leptomeningeal 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

Rituximab (Rituxan®) is considered investigational for the following off-label indication:

- Treatment of lymphoid B-cell malignancies that do not express CD20 antigen.

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

Ofatumumab (Arzerra®) may be considered medically necessary for the following off-label indication:

- Salvage treatment of Waldenstrom’s Macroglobulinemia/Lymphoplasmacytic lymphoma in rituximab-intolerant patients.
Adcetris®
Brentuximab vedotin may be considered medically necessary for the following labeled indications:

- Classical Hodgkin Lymphoma (HL) after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates.
- Classical HL at high risk of relapse or progression as post-auto-HSCT consolidation.
- Systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen.

Related 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

Policy Guidelines

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.

Coding

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<td>J9042</td>
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<tr>
<td>J9302</td>
<td>Injection, ofatumumab, 10 mg (Arzerra)</td>
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<td>J9310</td>
<td>Injection, rituximab, 100 mg (Rituxan)</td>
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<td>J9999</td>
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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.

Rituximab (Rituxan®) 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)

Ofatumumab (Arzerra®): 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 (e.g., 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 andatumumab.

**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 services representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
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.

Rationale

Rituximab (Rituxan®)

Regarding 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

Ofatumumab (Arzerra®)

The evidence for efficacy and safety of ofatumumab is currently limited to uncontrolled clinical studies. This evidence suggests ofatumumab is efficacious for achieving an objective response in approximately 50% patients with fludarabine- 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 (e.g., rituximab). In addition, improved survival remains to be established.

Brentuximab vedotin (Adcetris)

The efficacy of ADCETRIS 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.

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

The efficacy of ADCETRIS 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 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 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, 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 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 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.

**2004 Update**

The U.S. Pharmacopoeial Convention (2003) has concluded that rituximab (Rituxan) 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 Ofatumumab (Arzerra) NCCN recommended off-label use for Waldenstrom's macroglobulinemia. (Category 2A)

Alemtuzumab (Campath) 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.

References

1. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Off-label uses of monoclonal antibodies for treatment of B-cell lymphoid or myeloid malignancies. TEC Assessments 2001; Tab 7.
3. 2002 TEC Assessment; Tab 3, Rituximab for treatment of intermediate or aggressive B-cell non-Hodgkin’s lymphoma.


29. Ghielmini M, Hsu, Schmitz SF, Cogliatti SB; et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. Blood 2004; 103:4416-23.


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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.
12/13/16 Annual review. Adcetris® criteria, description, and rationale were added to the policy.
01/13/17 Coding update, added HCPCS code J9042.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA).
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Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
• Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  • Qualified sign language interpreters
  • Written information in other formats (large print, audio, accessible electronic formats, other formats)
• Provides free language services to people whose primary language is not English, such as:
  • Qualified interpreters
  • Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S909, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at

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 before 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).

Arabic (Amharic):
لم يوجد أي إخطار عناصر أمانة. يحتوي هذا الإخطار على معلومات هامة يقرره هدف المحصلة محدودة بشكل محدود. قد تكون هناك تأثير مؤقت. تسعى Premera Blue Cross لتعزيز تعديل هذه المعلومات بتلبية المستخدمين الذين يرغبون في تلقي هذه المعلومات في اللغة الأم. إعلان 800-722-1471 (TTY: 800-842-5357).

العربية (Arabic):
يوجد هذا الإخطار خدمات هامة. قد يكون هذا الإخطار معلومات يمكن أن تؤثر على طبيعة معلومات Premera Blue Cross. قد تكون هناك تأثير مؤقت. تسعى Premera Blue Cross لتعزيز تعديل هذه المعلومات بتلبية المستخدمين الذين يرغبون في تلقي هذه المعلومات في اللغة الأم. إعلان 800-722-1471 (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。本通知可能有重要的日期。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).

Oromo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):

Deutsche (German):

Hmoob (Hmong):
Tsaab ntawv tshaj xo no muaj cov ntsibh lius tseem ceeb. Tej jaum tsab ntawv tshaj xo no muaj cov ntsibh lius tseem ceeb bokoj kaj dain twaw thov keb pab los yoy koj qhov keb pab cuam los ntawm Premera Blue Cross. Tej jaum muaj cov hnbv tseem ceeb usas rau hauv daim ntawv no. Tej jaum koy koy juav tau uaa qee yam us peb koy us taa pis pub dhaa cov caj nyog uas teev tseg rau hauv daim niawv no mas koy thaj thay tuav baai keb pab cuam kho moob los yoy keb pab them tej nqj kho moob ntawv. Koy muaj cai kom laww muab cov ntsibh lius no uas tau muab sap uaa koy hom lus pub dawb rau koy. Hu rau 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):