LifeWise
Health Plan of Washington

MEDICAL POLICY – 2.03.502

Monoclonal Antibodies for the Treatment of Lymphoma

BCBSA Ref. Policy: 2.03.05

Effective Date:	**Jan. 3, 2025***
Last Revised:	Sept. 10, 2024
Replaces:	N/A

*Click here to view the current policy.

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

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | 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 to 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

Note: Rituxan (rituximab), Ruxience (rituximab-pvvr), Riabni (rituximab-arrx), and Truxima (rituximab-abbs) are not subject to Site of Service review when used for the treatment of lymphoma.

Drug	Medical Necessity

Ruxience (rituximab-pvvr), Truxima (rituximab-abbs)
• **First-line**
 	
Riabni (rituximab-arrx), Rituxan (rituximab)
• **Second-line**
	Rituxan (rituximab), Ruxience (rituximab-pvvr), Riabni (rituximab-arrx), and Truxima (rituximab-abbs) are a CD20-directed cytolytic antibody and may be considered medically necessary (for the following labeled indications) in the treatment of individuals with:
	• Non-Hodgkin's Lymphoma (NHL)
	• Chronic Lymphocytic Leukemia (CLL)
	AND
	• For Riabni (rituximab-arrx) and Rituxan (rituximab), the individual has had an inadequate response or intolerance to Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs)
	
	Rituxan (rituximab), Ruxience (rituximab-pvvr), Riabni (rituximab-arrx), and Truxima (rituximab-abbs) 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
	  ○ ALL, Chronic lymphocytic leukemia/small lymphocytic lymphoma (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

Drug	Medical Necessity
	○ Multiple myeloma ○ Waldenstrom's macroglobulinemia ○ 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 **AND** • For Riabni (rituximab-arrx) and Rituxan (rituximab), the individual has had an inadequate response or intolerance to Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs)
Rituxan Hycela (rituximab and hyaluronidase human)	**Rituxan Hycela (rituximab and hyaluronidase human) may be considered medically necessary for the treatment of adult individuals with documented CD20 antigen expression for the following conditions:** • 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 individuals 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 **AND** • Individual has had an inadequate response or intolerance to Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs)

Drug	Medical Necessity
	○ **Exception:** This may be granted when documentation is provided of difficult venous access. **Rituxan Hycela (rituximab and hyaluronidase human) may be considered medically necessary for any other labeled or off-label indications of Rituxan when the following criteria are met:** • The individual has had an inadequate response or intolerance to Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) ○ **Exception:** This may be granted when documentation is provided of difficult venous access. **Note**: Initiate treatment with Rituxan Hycela only after individuals 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 treatment of chronic lymphocytic leukemia (CLL):** • In combination with chlorambucil, for the treatment of previously untreated individuals with CLL for whom fludarabine-based therapy is considered inappropriate • In combination with fludarabine and cyclophosphamide for the treatment of individuals with relapsed CLL • For extended treatment of individuals who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL • For the treatment of individuals with 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 • Pediatric individuals 2 to less than 22 years of age with previously untreated high risk (Ann Arbor Stage IIB with bulk disease, Stage IIIB, Stage IVA, and Stage IVB) classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide (AVE-PC)

Drug	Medical Necessity
	• 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 individuals who are not auto-HSCT candidates • Previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with chemotherapy • 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 CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy
Columvi (glofitamab-gxbm)	**Columvi (glofitamab-gxbm) may be considered medically necessary for:** • Treatment of adult individuals with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) or large B-cell lymphoma (LBCL) arising from follicular lymphoma, after two or more lines of systemic therapies. **AND** • Documentation of pretreatment with a single 1,000mg dose of obinutuzumab intravenously 7 days before initiation of Columvi
Epkinly (epcoritamab-bysp)	**Epkinly (epcoritamab-bysp) may be considered medically necessary for the treatment of adult individuals with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) if all of the following are met:** • The individual is aged 18 years and older **AND** • Has relapsed or refractory DLBCL, not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy

Drug	Medical Necessity
	Epkinly (epcoritamab-bysp) may be considered medically necessary for the treatment of relapsed and refractory follicular lymphoma (FL) in individuals aged 18 years and older when: • Two or more lines of systemic therapy have been tried and failed
Lunsumio (mosunetuzumab-axgb)	**Lunsumio (mosunetuzumab-axgb) may be considered medically necessary for the following labeled indication:** • Treatment of adult individuals with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy
Monjuvi (tafasitamab-cxix)	**Monjuvi (tafasitamab-cxix) may be considered medically necessary when all the following are met:** • Monjuvi (tafasitamab-cxix) will be used in combination with lenalidomide for the treatment of adult individuals with relapsed or refractory DLBCL not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT) **AND** • The individual has tried at least two prior therapies to treat DLBCL
Polivy (polatuzumab vedotin-piiq)	**Polivy (polatuzumab vedotin-piiq) may be considered medically necessary for the following labeled indication:** • In combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult individuals who have previously untreated diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS) or high-grade B-cell lymphoma (HGBL), and who have an International Prognostic Index (IPI) score of 2 or greater • In combination with bendamustine and a rituximab product for the treatment of adult individuals with relapsed or refractory DLBCL, not otherwise specified, after at least two prior therapies

Drug	Investigational
Rituxan (rituximab),	**Rituxan (rituximab), Rituxan Hycela (rituximab and hyaluronidase human), Ruxience (rituximab-pvvr), Riabni**

Drug	Investigational
Rituxan Hycela (rituximab and hyaluronidase human), Ruxience (rituximab-pvvr), Riabni (rituximab-arrx), Truxima (rituximab-abbs)	**(rituximab-arrx), and Truxima (rituximab-abbs) are considered investigational for the following off-label indication:** • Treatment of lymphoid B-cell malignancies that do not express CD20 antigen **All other uses of Rituxan (rituximab), Rituxan Hycela (rituximab and hyaluronidase human), Ruxience (rituximab-pvvr), Riabni (rituximab-arrx), and Truxima (rituximab-abbs) are considered investigational unless listed in a related medical policy.**
As listed	**All other uses of the medications listed in this policy are considered investigational.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**All drugs listed in policy may be approved up to 6 months.**
Re-authorization criteria	**Future re-authorization of all drugs listed in policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation and medication history

Coding

Code	Description
HCPCS	

Code	Description
C9155	Injection, epcoritamab-bysp, 0.16 mg (Epkinly) (code termed effective 1/1/2024)
J3590	Unclassified biologics (Columvi)
J9042	Injection, brentuximab vedotin (Adcetris), 1 mg
J9286	Injection, glofitamab-gxbm, 2.5 mg (Columvi) (new code effective 1/1/2024)
J9302	Injection, ofatumumab (Arzerra), 10 mg
J9309	Injection, polatuzumab vedotin-piiq (Polivy), 1 mg
J9311	Injection, rituximab 10 mg and hyaluronidase (Rituxan Hycela)
J9312	Injection, rituximab, 10 mg (Rituxan)
J9313	Injection, moxetumomab pasudotox-tdfk, (Lumoxiti) 0.01 mg
J9321	Injection, epcoritamab-bysp, 0.16 mg (Epkinly) (new code effective 1/1/2024)
J9349	Injection, tafasitamab-cxix, (Monjuvi) 2 mg
J9350	Injection, mosunetuzumab-axgb, (Lunsumio), 1 mg
Q5115	Injection, rituximab-abbs, biosimilar, (Truxima), 10 mg
Q5119	Injection, rituximab-pvvr, biosimilar, (Ruxience), 10 mg
Q5123	Injection, rituximab-arrx, biosimilar, (Riabni), 10 mg)

Related Information

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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.

Benefit Application

This policy is managed through the medical benefit.

International Prognostic Index

One point is given for each of the characteristics below in the individual for a total score ranging from zero to five.

- 60 years of age or older
- Serum lactate dehydrogenase concentration above normal
- Eastern Cooperative Oncology Group (ECOG) performance status of 2 or greater
- Ann Arbor stage III or IV
- Number of extranodal disease sites greater than 1

Table 1. Eastern Cooperative Oncology Group (ECOG)

Performance Status	Definition
0	Fully active; no performance restrictions.
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work.
2	Capable of all self-care but unable to carry out any work activities. Up and about greater than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair greater than 50% of waking hours.
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

Table 2. Ann Arbor Revised Staging System for Primary Nodal Lymphomas

Stage	Involvement	Extranodal Status
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky	II as above with “bulky” disease	Not applicable

Stage	Involvement	Extranodal Status
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

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 individuals 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 individuals 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 individuals with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab.

Brentuximab vedotin is an antibody-drug conjugate (ADC). The antibody is a chimeric IgG1 directed against CD30. The small molecule, monomethyl auristatin E (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 systematic anaplastic large cell lymphoma (sALCL) cells and on Hodgkin Reed-Sternberg (HRS) cells in classical Hodgkin's lymphoma (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.

Moxetumomab pasudotox-tdfk is a CD22-directed cytotoxin. Moxetumomab pasudotox-tdfk binds CD22 on the cell surface of B-cells and is internalized. Moxetumomab pasudotox-tdfk internalization results in ADP-ribosylation of elongation factor 2, inhibition of protein synthesis, and apoptotic cell death.

Lunsumio (mosunetuzumab-axgb) is a T-cell engaging bispecific antibody that binds to the CD3 receptor expressed on the surface of T-cells and CD20 expressed on the surface of lymphoma cells and some healthy B-lineage cells. In vitro, mosunetuzumab-axgb activated T-cells, caused the release of proinflammatory cytokines, and induced lysis of B-cells.

National Comprehensive Cancer Network 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 that the intervention is appropriate

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

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 individuals with intermediate or aggressive 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 individuals with previously treated diffuse large B-cell lymphoma. By intent–to-treat analysis, event-free and overall survival (OS) 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 individuals with intermediate or aggressive B-cell non-Hodgkin's lymphoma based on the Coiffier study.

In a randomized, Phase III trial of 122 individuals with untreated advanced-stage mantle cell lymphoma, Lenz and colleagues reported individuals receiving cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) plus rituximab (n=62) had significantly superior outcomes than individuals 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 individuals 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 difference of -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 individuals 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 individuals 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 individuals 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% individuals with fludrabine- or alemtuzumab-refractory CLL.

The drug also appears to have efficacy in some individuals 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.

Adcetris (brentuximab vedotin)

Clinical Trial in Relapsed Classical HL (Study 1)

The efficacy of Adcetris (brentuximab vedotin) in individuals with classical HL who relapsed after autologous hematopoietic stem cell transplantation (HSCT) was evaluated in one open-label, single-arm, multicenter trial. One hundred two individuals 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 individuals ranged in age from 15–77 years (median, 31 years) and most were female (53%) and white (87%). Individuals had received a median of 5 prior therapies including autologous HSCT hematopoietic stem cell transplantation. Duration of response is calculated from date of first response to date of progression or data cutoff date. The CR was 32% (95% CI; 23% – 42%), PR was 40% (95% CI; 32% – 49%), and the ORR was 73% (95% CI; 65% – 83%).

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

The efficacy of Adcetris (brentuximab vedotin) in individuals 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 individuals 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. Individuals 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.

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

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

age from 18–76 years (median, 32 years) and most were male (53%) and white (94%). Individuals 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 OS analysis demonstrated no difference.

Clinical Trial in Relapsed sALCL (Study 2)

The efficacy of Adcetris (brentuximab vedotin) in individuals with relapsed sALCL was evaluated in one open-label, single-arm, multicenter trial. This trial included individuals who had sALCL that was relapsed after prior therapy. Fifty-eight individuals 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 individuals ranged in age from 14–76 years (median, 52 years) and most were male (57%) and white (83%). Individuals had received a median of 2 prior therapies; 26% of individuals had received prior autologous hematopoietic stem cell transplantation. Fifty percent (50%) of individuals were relapsed and 50% of individuals 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.

Columvi (glofitamab-gxbm)

The efficacy of Columvi (glofitamab-gxbm) was evaluated in an open-label, multicenter, multicohort, single-arm clinical trial which included 132 individuals with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy. The inclusion criteria required individuals to have ECOG performance status of 0 or 1, absolute neutrophil count greater than or equal to 1500/µL, platelet count greater than or equal to 75,000 /µL independent of transfusion, serum creatinine less than or equal to 1.5 x ULN or CLcr greater

than or equal to 50 ml/min, hepatic transaminases less than or equal to 3 x ULN. The individuals required to have pretreatment with Obinutuzumab on Cycle 1 Day 1.

The primary efficacy endpoint was objective response rate (ORR) and duration of response (DOR). The overall response rate was 56% for the Columvi group, where 43% individuals had complete response and 13% individuals had partial response. Out of 74 individuals with overall response, median duration of response was 18.4 months.

The most common adverse effects included cytokine release syndrome, musculoskeletal pain, rash and fatigue. The most common Grade 3 to 4 laboratory abnormalities are reduced lymphocyte counts, reduced phosphate level, reduced neutrophil count, increased uric acid and reduced fibrinogen. Treatment related adverse events which led to permanent discontinuation in the Columvi group included infection, delirium, neutropenia, and CRS. Also, adverse events which led to dose interruption included neutropenia and thrombocytopenia.

Epkinly (epcoritamab-bysp)

The Phase 1/2 EPCORE NHL-1/Study GCT3013-01 (NCT03625037) trial was an open-label, multicohort, multicenter, single-arm study involving individuals with relapsed or refractory (R/R) B-cell lymphoma. The efficacy population included 148 individuals with DLBCL, not otherwise specified (NOS), including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma. The study excluded individuals with central nervous system (CNS) involvement of lymphoma, allogeneic hematopoietic stem cell transplant (HSCT) or solid organ transplant, or ongoing active infection, and any individuals with known impaired T-cell immunity. Individuals received Epkinly subcutaneously (SC) with Cycle 1 step-up dosing consisting of a 0.16 mg priming dose once on Day 1, followed by an 0.8 mg intermediate dose once on Day 8, and subsequent full 48 mg doses once on Day 15 and Day 22. Cycles were every 28 days. On Cycles 2 and 3, individuals received 48 mg on Days 1, 8, 15, and 22. On Cycles 4–9, individuals received 48 mg on Days 1 and 15. From Cycle 10 and beyond, individuals received 48 mg once every 28 days. Individuals continued to receive Epkinly until disease progression or unacceptable toxicity. In the setting of a suspected tumor flare reaction, continued treatment was permitted. The primary efficacy measure of the study was the overall response rate (ORR) assessed according to the Lugano 2014 criteria by an independent review committee. The ORR was determined to be 61% (95% CI: 53, 69), with 38% of individuals achieving complete responses. Among responders, with a median follow-up of 9.8 months, the estimated median duration of response (DOR) was 15.6 months (95% confidence interval [CI]: 9.7, not reached). The median time to response was 1.4 months (range: 1.0 to 8.4 months). Among responders, the median follow-up for DOR was 9.8 months (range: 0.0 to 17.3 months). The prescribing information has a Boxed Warning for

serious or life-threatening cytokine release syndrome (CRS) and life-threatening or fatal immune effector cell-associated neurotoxicity syndrome (ICANS). Warnings and precautions include infections and cytopenias. In the full EPCORE NHL-1 clinical trial involving 157 individuals with R/R large B-cell lymphoma who received Epkinly at the recommended dose, CRS occurred in 51% of individuals, ICANS in 6%, and serious infections in 15%. It is emphasized that Epkinly should only be administered by a qualified healthcare professional with appropriate medical support to manage severe reactions such as CRS and ICANS. Due to the risk of these reactions, individuals should be hospitalized for 24 hours following the Cycle 1, Day 15 dosage of 48 mg. The most frequently reported adverse reactions associated with Epkinly include CRS, fatigue, musculoskeletal pain, injection site reactions, fever, abdominal pain, nausea, and diarrhea. The most common Grade 3 to 4 laboratory abnormalities observed were decreased lymphocyte count, decreased neutrophil count, decreased white blood cell count, decreased hemoglobin, and decreased platelets.

Lumoxiti (moxetumomab pasudotox)

The efficacy of Lumoxiti (moxetumomab pasudotox) was based upon a pivotal multicenter trial of Moxetumomab Pasudotox in relapsed/refractory Hairy Cell Leukemia, conducted in individuals with histologically confirmed HCL or HCL variant with a need for therapy based on presence of cytopenias or splenomegaly and who had received prior treatment with at least 2 systemic therapies, including 1 purine nucleoside analog (PNA). Eligible individuals had serum creatinine less than or equal to 1.5 mg/dL or creatinine clearance greater than or equal to 60 mL/min as estimated by the Cockcroft Gault equation.

A total of 80 individuals were enrolled: 77 with classic HCL and 3 with HCL variant. The median age was 60 years (range: 34 to 84) years, 79% were male, and 94% were Caucasian. At baseline, 98% of individuals had an ECOG performance status of 0 or 1. The median number of prior treatments was 3 (range: 2 to 11); all individuals received prior PNA therapy, including 29% in combination with rituximab. The most common other prior treatment regimens were rituximab monotherapy (51%), interferon-alpha (25%), and a BRAF inhibitor (18%). At baseline, 33% (26/80) of individuals had low hemoglobin (less than 10 g/dL), 68% (54/80) of individuals had neutropenia (less than 1000/mm^3), and 84% (67/80) individuals had baseline platelet counts less than 100,000/mm^3. About 35% of individuals had enlarged spleens (greater than or equal to 14 cm, assessed by BICR) at baseline.

Individuals received moxetumomab pasudotox 0.04 mg/kg as an intravenous infusion over 30 minutes on Days 1, 3, and 5 of each 28-day cycle for a maximum of 6 cycles or until documentation of complete response (CR), disease progression, or unacceptable toxicity. The

median duration of follow-up was 16.7 months (range: 2 to 49). An independent review committee (IRC) performed efficacy evaluations using blood, bone marrow, and imaging criteria adapted from previous HCL studies and consensus guidelines. Efficacy of moxetumomab pasudotox in HCL was evaluated by the IRC-assessed rate of durable CR, as confirmed by maintenance of hematologic remission (hemoglobin greater than or equal to 11 g/dL, neutrophils greater than or equal to 1500/mm^3, and platelets greater than or equal to 100,000/mm^3 without transfusions or growth factor for at least 4 weeks) more than 180 days after IRC-assessed CR. The IRC-assessed durable CR rate was 30% (24/80 individuals; 95% CI: 20, 41).

Monjuvi (tafasitamab-cxix)

Phase 2/3 evidence for the efficacy and safety of tafasitamab for relapsed/refractory (R/R) DLBCL consists of two fair quality Phase 2 trials, one in combination with lenalinomide and the other as monotherapy.

L-MIND was an international, single-arm, open-label, Phase 2 trial in 81 adults with R/R DLBCL who were ineligible for high-dose chemotherapy and hematopoietic stem cell therapy (HSCT). Eligible individuals received tafasitamab + lenalidomide for 12 (28-day) cycles, followed by tafasitamab maintenance monotherapy until progressive disease (PD) in individuals with at least stable disease (SD). The primary study endpoint was objective response rate (CR + PR) (ORR). Results showed an ORR of 60%, with 43% complete response (CR) and 18% partial response (PR). Secondary outcomes included an SD of 16%, disease control rate (CR + PR + SD) (DCR) of 74%, duration of response (DOR) of 22 months, median progression-free survival (PFS) of 12 months, time to first subsequent therapy (TFST) of 15 months, and median OS was not reached (at a median 19.6 months follow-up).

In second fair quality, multicenter, single-arm, open-label, Phase 2a study, 92 adults with R/R NHL, including a cohort of 35 with R/R DLBCL, received tafasitamab weekly for 8 weeks, then those with at least SD received additional weekly doses for 4 more weeks, then those with CR or PR could continue Q2W or monthly maintenance therapy until PD. The primary study endpoint was ORR. In the DLBCL cohort, ORR was 26%, with n=2 CR and n=7 PR. Secondary outcomes included a SD of 14%, a median DOR of 20 months, and median PFS was 2.7 months (after a median follow-up of 21 months).

Indirect comparison of the L-MIND response rate with that for lenalidomide and tafasitamab monotherapy in R/R NHL (including DLBCL) (28-35% and 26%, respectively) suggests tafasitamab + lenalidomide may be more efficacious than either agent alone. However, the

response rate for available CAR T-cell therapies ranges from 52%-82% and for polatuzumab + bendamustine + rituximab was 45%, with 40% achieving CR.

Polivy (polatuzumab vedotin-piiq)

Evidence from one ongoing, global, randomized, active-controlled Phase Ib/II trial currently supports the proposed indication of use in combination with bendamustine/rituximab (BR) for the treatment of adults with relapsed/refractory (R/R) DLBCL. As of a data cutoff of April 30, 2018 and a median follow-up of 22.3 months, positron emission tomography complete response (PET-CR) by independent review committee (IRC) was 40% with polatuzumab + BR vs 18% with BR (NNT=4.5) and ORR was 45% vs 18% (NNT=3.7), respectively. While exploratory endpoints in the trial, progression-free survival (PFS) and OS also appeared longer with polatuzumab + BR compared to BR.

In an additional multicenter, randomized, open-label, active-controlled Phase II trial (ROMULUS), the antitumor activity and safety of polatuzumab + rituximab was compared with that of pinatuzumab + rituximab in individuals with R/R DLBCL or R/R FL. Both antibody drug conjugate (ADCs) were administered as 2.4 mg/kg IV every 21 days (each cycle) in combination with rituximab until PD, unacceptable toxicity, or up to one year. The primary study outcomes were anti-tumor response and safety. A total of 81 individuals with DLBCL were randomized to polatuzumab + rituximab (n=39) or pinatuzumab (n=42) and a total of 41 individuals with FL were randomized to polatuzumab + rituximab (n=20) or pinatuzumab + rituximab (n=21).

In an ongoing, multicenter, open-label, single arm, Phase Ib/II (dose escalation/expansion) trial, the preliminary antitumor activity and safety of polatuzumab (1.8 mg/kg) in combination with rituximab or obinutuzumab (G; 1.4 mg/kg) IV plus cyclophosphamide/doxorubicin/prednisone (CHP) every 21 days (each cycle) for 6-8 cycles was evaluated in treatment-naïve individuals with DLBCL. The primary study outcomes were safety and maximum tolerated dose. Preliminary antitumor activity (ORR, CR, PFS, and OS) was a secondary study outcome. A total of 82 individuals were treated and evaluated, n=25 with any previously untreated B-cell NHL in the dose escalation phase and n=57 with previously untreated DLBCL and an International Prognostic Index (IPI) of 2-5 in the dose expansion cohort. The maximum tolerated dose of polatuzumab + R/G-CHP from Phase Ib was 1.8 mg/kg every 21 days; consequently, this was the dose employed in the Phase II dose expansion phase. At a December 29, 2017 data cutoff in the dose expansion phase, 75 (91%) individuals had DLBCL and 66 (88%) of these 75 (n=45 R-CHP and n=21 G-CHP) were treated with the Phase Ib recommended polatuzumab dose of 1.8 mg/kg. Median follow-up was 21.5 months in this latter group. ORR was achieved by 59/66 (89%), with 51 (77%) having CR and 8 (12%) with PR. Also, in this subpopulation 12-Month PFS

was 91% (95% CI 84-98) and 24-month PFS was 83 (95% CI 73-93). Four individuals with untreated DLBCL receiving the recommended dose of polatuzumab during the expansion phase died [n=2 (3%) due to AEs (atrial fibrillation and septic shock) and n=2 (3%) due to disease progression].

Lunsumio (mosunetuzumab-axgb)

The efficacy of Lunsumio (mosunetuzumab-axgb) was evaluated in an open-label, multicenter, multi-cohort study (GO29781, NCT02500407) in individuals with relapsed or refractory follicular lymphoma (FL) who had received at least two prior therapies, including an anti-CD20 monoclonal antibody and an alkylating agent. The study excluded individuals with active infections, history of autoimmune disease, prior allogeneic transplant, or any history of CNS lymphoma or CNS disorders.

Individuals received step-up doses of 1 mg on Cycle 1 Day 1 and 2 mg on Cycle 1 Day 8, followed by 60 mg on Cycle 1 Day 15, and 60 mg on Cycle 2 Day 1, then 30 mg every 3 weeks in subsequent cycles. A treatment cycle was 21 days. Lunsumio was administered for 8 cycles unless individuals experienced progressive disease or unacceptable toxicity. After 8 cycles, individuals with a complete response discontinued therapy; individuals with a partial response or stable disease continued treatment up to 17 cycles, unless individuals experienced progressive disease or unacceptable toxicity.

Among the 90 individuals with relapsed or refractory FL, the median age was 60 years (range: 29 to 90 years), 33% were 65 years of age or older, 61% were male, 82% were White, 9% were Asian, 4% were Black or African American, and 8% were Hispanic or Latino. A total of 77% of individuals had Stage III-IV disease, 34% had bulky disease, and all individuals had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The median number of prior therapies was 3 (range: 2 to 10), with 38% receiving 2 prior therapies, 31% receiving 3 prior therapies, and 31% receiving more than 3 prior therapies.

Seventy-nine percent of individuals were refractory to prior anti-CD20 monoclonal antibody therapy, 53% were refractory to both anti-CD20 monoclonal antibody and alkylator therapy, 9% received prior rituximab plus lenalidomide therapy, 21% received prior autologous stem cell transplant, and 3% received prior CAR T therapy. Fifty-two percent of individuals had progression of disease within 24 months of first systemic therapy.

Efficacy was established on the basis of objective response rate (ORR) and duration of response (DOR) as assessed by an independent review facility according to standard criteria for NHL (Cheson 2007). The median follow-up for DOR was 14.9 months. The ORR was achieved in 80%

(95% CI: 70%, 88%) of individuals and the median DOR was 22.8 months (95% CI: 10 months, not reached).

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

2004 Update

The US 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 individuals 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 individuals.

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 individuals with symptomatic 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 individuals. 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 individuals with known cardiac history, omission of anthracyclines is reasonable and R-CVP provides a competitive CR rate. In younger individuals 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 individuals 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 individuals 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.

2018 Update

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

2019 Update

Reviewed prescribing information for all drugs in policy. Added criteria for the biosimilar Ruxience (rituximab-pvvr). Added criteria for a new medication Polivy (polatuzumab vedotin-piiq) for the treatment of relapsed or refractory DLBCL. No additional evidence was identified that would require changes to other drugs listed in this policy.

2020 Update

Reviewed prescribing information for all drugs in policy. No new evidence found that would change this policy.

2021 Update

Reviewed prescribing information for all drugs in policy. No new evidence found that would change this policy.

2022 Update

Reviewed prescribing information for all drugs in policy. No new evidence found that would change this policy.

2023 Update

Reviewed prescribing information for all drugs in policy. Updated Polivy criteria to indicate coverage in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult individuals who have previously untreated diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS) or high-grade B-cell lymphoma

(HGBL), and who have an International Prognostic Index (IPI) score of 2 or greater. Added coverage criteria for Columvi for the treatment of adult individuals with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified (DLBCL,NOS) or large B-cell lymphoma (LBCL) arising from follicular lymphoma, after two or more lines of systemic therapies. Updated Ruxience (rituximab-pvvr) to a non-preferred product. Removed Lumoxiti criteria as Astrazenenca has decided to permanently discontinue Lumoxiti from the US market and will not be available after August 2023. Updated Rituxan Hycela (rituximab and hyaluronidase) to require documentation of CD20 antigen expression. Added coverage criteria for Epkinly (epcoritamab-bysp) for the treatment of certain adults with diffuse large B-cell lymphoma (DLBCL).

2024 Update

Reviewed prescribing information for all drugs in policy. No new evidence found that would change this policy.

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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 individuals, or others who are not good candidates for cytotoxic chemotherapy" as a medically necessary indication. Policy

Date	Comments
	reviewed and recommended by OAP May 22, 2008. P&T reviewed and approved on May 27, 2008.
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 leptomeningeal 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 individuals; 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 individuals 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.

Date	Comments
01/01/17	Annual Review, approved December 13, 2016. Adcetris criteria, description, and rationale were added to the policy.
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.
12/01/18	Annual Review, approved November 13, 2018. Lumoxiti (moxetumomab pasudotox) added. Added HCPCS code J9999.
01/01/19	Coding update, added new HCPCS codes J9311 and J9312 (new codes effective 1/1/19).
02/01/19	Interim Review, approved January 8, 2019. Updated Adcetris indications.
05/01/19	Interim Review, approved April 18, 2019. Added criteria for Truxima (rituximab-abbs) which is a biosimilar of Rituxan (rituximab). Added description Rituxan Hycela to J9311 and Rituxan to J9312 in coding section. Added Truxima and Lumoxiti names in relationship to J9999. Added term date to HCPCS code J9310.
08/01/19	Coding update, added HCPCS code Q5115 (new code effective 7/1/19).
10/01/19	Coding update, added HCPCS code J9313 (new code effective 10/1/19). Removed HCPCS code J9999.
01/01/20	Annual Review, approved December 17, 2019, effective for dates of services on or after April 3, 2020, following provider notification. Added criteria for Polivy (polatuzumab vedotin-piiq). Added criteria for Ruxience (rituximab-pvvr) which is a biosimilar of Rituxan (rituximab). Updated criteria for Truxima (rituximab-abbs). Removed HCPCS code J9310 as it was terminated 1/1/19. Added HCPCS code J9309 (new code effective 1/1/20) and J3590 to report Ruxience. References were added.
07/01/20	Coding update. Added HCPCS code Q5119, removed HCPCS code J3590.
10/01/20	Annual Review, approved September 1, 2020. No change to policy statements.
12/01/20	Interim Review, approved November 10, 2020. Added coverage criteria for Monjuvi (tafasitamab-cxix) for the treatment of DLBCL. Added HCPCS code J3590 for Monjuvi.
01/01/21	Coding update. Added HCPCS code C9070.
02/01/21	Interim Review, approved January 21, 2021. Added the biosimilar Riabni (rituximab-arrx) as a second line product. Added Riabni to J3590.
04/01/21	Coding update, added term date to HCPC C9070 and added new HCPC code J9349.
07/01/21	Coding update, Added HCPCS code Q5123.

Date	Comments
09/01/21	Annual Review, approved August 3, 2021. No change to policy statements.
07/01/22	Interim Review, approved June 14, 2022. Moved Truxima (rituximab-abbs) to being a preferred rituximab product. Updated coverage criteria for the non-preferred product Riabni (rituximab-arrx) to require the individual has had an adequate trial and failure with Rituxan, Ruxience, or Truxima. Removed HCPCS codes C9070 and J3590.
12/01/22	Annual Review, approved November 21. 2022. No change to policy statements. Changed the wording from "patient" to "individual" throughout the policy for standardization.
02/01/23	Interim Review, approved January 10, 2023. Added a new indication to Adcetris (brentuximab vedotin) for the treatment of individuals 2 to less than 22 years of age with previously untreated high risk cHL in combination with chemotherapy. Added coverage for Lunsumio (mosunetuzumab-axgb) for the treatment of relapsed or refractory follicular lymphoma. Added HCPC code J3590 for Lunsumio.
06/01/23	Annual Review, approved May 9, 2023. Updated Polivy criteria to indicate coverage in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult individuals who have previously untreated diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS) or high-grade B-cell lymphoma (HGBL), and who have an International Prognostic Index (IPI) score of 2 or greater.
07/01/23	Coding update. Added new HCPCS code J9350.
08/01/23	Interim Review, approved July 11, 2023. Added coverage criteria for Columvi for the treatment of adult individuals with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified (DLBCL,NOS) or large B-cell lymphoma (LBCL) arising from follicular lymphoma, after two or more lines of systemic therapies. Updated Related Policies, removed 8.01.533 as it was archived.
09/01/23	Interim Review, approved August 8, 2023. Removed Lumoxiti criteria as Astrazenenca has decided to permanently discontinue Lumoxiti from the US market and will not be available after August 2023. Updated Ruxience (rituximab-pvvr) to a non-preferred product, effective January 1, 2024, following a 90-day provider notification due to changes in the preferred medical benefit drugs.
01/01/24	Interim Review, approved December 12, 2023. Updated Rituxan Hycela (rituximab and hyaluronidase) to require documentation of CD20 antigen expression. Added coverage criteria for Epkinly (epcoritamab-bysp) for the treatment of certain adults with diffuse large B-cell lymphoma (DLBCL), effective April 4, 2024, following a 90-day provider notification. Added HCPCS codes C9155, J9321 and J9286 and termed HCPCS code C9155.
08/01/24	Annual Review, approved July 22, 2024. No change to policy statements.
10/01/24	Interim Review, approved September 10, 2024. Added a new indication to Epkinly (epcoritamab-bysp) for the treatment of adult individuals with relapsed or refractory FL. The following policy changes are effective January 3, 2025, following a 90-day

Date	Comments
	provider notification. Changed Ruxience (rituximab-pvvr) to a preferred rituximab product. Changed Rituxan (rituximab) and Rituxan Hycela (rituximab and hyaluronidase human) to non-preferred rituximab products. Updated coverage criteria for Riabni (rituximab-arrx), Rituxan, and Rituxan Hycela to require the individual has had an adequate trial and failure with Ruxience or Truxima.

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.