

Corporate Medical Policy

Monoclonal Antibodies for Non-Hodgkin Lymphoma and Acute Myeloid Leukemia In the Non-Hematopoietic Stem Cell Transplant Setting

“Notification”

File Name:	monoclonal_antibodies_for_non_hodgkin_lymphoma_acute_myeloid_leukemia
Origination:	7/2009
Last CAP Review:	4/2020
Next CAP Review:	4/2021
Last Review:	1/2021

Policy Effective April 1, 2021

Description of Procedure or Service

Monoclonal antibodies targeted to cancer-associated antigens have been approved by the U.S. Food and Drug Administration (FDA) for various uses in oncology. In some cases, these agents are used in settings outside of the FDA-approved label (i.e., off-label use).

C20-Directed Cytolytic Antibodies

C20 is a cell surface antigen expressed on pre B- and mature B-lymphocytes. More than 90% of malignant B-cells in non-Hodgkin lymphoma (NHL) express CD20. CD20- directed cytolytic antibodies mediate cell lysis by antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and induction of intracellular death signaling pathways (apoptosis). All 3 CD20-directed cytolytic antibodies (i.e. Rituxan, Arzerra, Gazyva) carry black box warnings for hepatitis B virus reactivation and progressive multifocal leukoencephalopathy.

- Rituximab (Rituxan®) is a chimeric murine/human monoclonal antibody. In addition to inducing B-cell lysis, rituximab sensitizes B cells to the cytotoxic effect of chemotherapy. Rituximab also carries black box warnings for serious, potentially fatal, infusion reactions and severe mucocutaneous reactions.
- Rituxan Hycela™ is a combination of rituximab, a CD20-directed cytolytic antibody, and hyaluronidase human, an endoglycosidase, indicated for the treatment of adult patients with follicular lymphoma, diffuse large B-cell lymphoma and chronic lymphocytic leukemia.
- Ofatumumab (Arzerra®) is also a fully human monoclonal antibody produced in a recombinant murine cell line. Ofatumumab targets an epitope that differs from the binding location of rituximab. In chronic lymphocytic leukemia (CLL), B cells underexpress CD20; unlike rituximab, which depends on CD20 expression for complement-dependent cytotoxicity, ofatumumab does not appear to depend on antigen intensity.
- Obinutuzumab (Gazyva™) is a humanized monoclonal antibody produced in Chinese hamster ovary cell culture. In addition to the cytolytic mechanisms described above, obintuzumab induces antibody-dependent cellular phagocytosis.
- Gemtuzumab Ozogamicin (Mylotarg™) is a CD33-directed antibody-drug conjugate indicated for treatment of newly-diagnosed CD33-positive acute myeloid leukemia (AML) in adults and treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older.

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This policy considers labeled and off-label indications for the uses of rituximab, ofatumumab, and obinutuzumab, in NHL in the non-hematopoietic stem-cell transplant setting.

For non-oncologic uses of rituximab, please see BCBSNC Corporate Medical Policy, “Rituximab for the Treatment of Rheumatoid Arthritis.”

Regulatory status

Rituximab (Rituxan) was initially approved by the U.S. Food and Drug Administration (FDA) on November 26, 1997 for the treatment of relapsed or refractory low-grade or follicular, CD20-positive, B-cell NHL. Since 1997, rituximab has gained additional oncologic and non-oncologic indications. Current FDA-approved oncologic indications of rituximab include follicular NHL, diffuse large B-cell lymphoma (DLBCL), and CLL.

In June 2017, a subcutaneous form of rituximab with hyaluronidase human (Rituxan Hycela) was approved by the FDA. The medication combines rituximab and hyaluronidase human. Human hyaluronidase was included to temporarily degrade the extracellular matrix and facilitate the absorption of larger volumes of rituximab. Rituxan Hycela™ is approved for follicular NHL, diffuse large B-cell lymphoma (DLBCL), and CLL, in patients who have already received at least one full dose of intravenous rituximab.

On October 26, 2009, the U.S. Food and Drug Administration granted accelerated approval to ofatumumab (Arzerra) for the treatment of patients with CLL refractory to fludarabine and alemtuzumab. Full approval was contingent on results of a Phase 3 trial “intended to verify the clinical benefit of ofatumumab through demonstration of a clinically meaningful effect on progression-free survival.” On April 17, 2014, FDA converted the accelerated approval to full approval and added the indication, “in combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate.

Obinutuzumab (Gazyva) is the first Breakthrough Therapy-designated drug to receive FDA approval, which was granted on November 1, 2013. The approved indication is for treatment of patients with previously untreated CLL in combination with chlorambucil. As of February 2016, Gazyva, in combination with bendamustine, followed by Gazyva monotherapy, is indicated for the treatment of patients with follicular lymphoma who relapsed after, or are refractory to, a rituximab-containing regimen.

In November 2013, obinutuzumab (Gazyva) was approved by FDA through the breakthrough therapy designation process for treatment of patients with previously untreated CLL in combination with chlorambucil. In February 2016, the drug was approved, in combination with bendamustine followed by obinutuzumab monotherapy, for the treatment of patients with follicular lymphoma who relapsed or are refractory to a rituximab-containing regimen.

The following biosimilars to rituximab have been approved by the FDA for the same labeled oncologic indications as the parent drug, Rituxan (rituximab), for the treatment of B-cell non-Hodgkin’s lymphoma (NHL) and chronic lymphocytic leukemia:

- FDA approved November 2018, Truxima® (rituximab-abbs; Teva)
- FDA approved July 2019, Ruxience™ (rituximab-pvvr; Pfizer)
- FDA approved December 2020, Riabni™ (rituximab-arrx; Amgen)

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

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Policy

BCBSNC will provide coverage for Monoclonal Antibodies for Non-Hodgkin Lymphoma and Acute Myeloid Leukemia when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Monoclonal Antibodies for Non-Hodgkin Lymphoma and Acute Myeloid Leukemia are covered

1. Rituximab (Rituxan) and rituximab biosimilars (rituximab-abbs, rituximab-arrx, rituximab-pvvr) may be considered medically necessary when the following criteria are met:
 - a. For the treatment of patients with B-cell non-Hodgkin's lymphoma (NHL) in any of the following clinical situations:
 - i. Follicular lymphoma:
 - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy*
 - Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent, after first-line CVP (cyclophosphamide, vincristine, prednisolone) chemotherapy*
 - Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent*
 - ii. Diffuse large B-cell lymphoma:
 - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or other anthracycline-based chemotherapy*
 - iii. B-cell chronic lymphocytic leukemia (B-CLL):
 - Previously untreated and previously treated CD20-positive CLL in combination with FC (fludarabine and cyclophosphamide)*
 - iv. CD20-positive NHL:
 - Recurrent or aggressive
 - v. Mantle cell lymphoma:
 - As first-line therapy in combination with one of guideline-based chemotherapy regimens
 - Relapsed or refractory maintenance therapy until progression or intolerance
 - vi. Burkitt lymphoma:
 - As first-line therapy
 - vii. Post-transplant lymphoproliferative disorders:
 - For patients who have had an inadequate response to reduction of immunosuppression or are not candidates for reduction of immunosuppression and have Castleman's disease (NCCN 2A); **AND**
 - b. If the request is for rituximab (Rituxan) or non-preferred rituximab biosimilars (e.g., rituximab-arrx), then both of the following criteria are met:

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- i. The patient has a documented serious adverse event that required medical intervention to both preferred rituximab biosimilar products [rituximab-abbs (Truxima), rituximab-pvvr (Ruxience)] that is not anticipated with the requested product; **AND**
 - ii. The prescriber has completed and submitted an FDA MedWatch Adverse Event Reporting Form
2. Rituxan Hycela may be considered medically necessary to treat patients in any of the following clinical situations:
 - a. Follicular Lymphoma
 - Relapsed or refractory, follicular lymphoma as a single agent*
 - Previously untreated follicular lymphoma in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as a single agent maintenance therapy*
 - Non-progressing (including stable disease), follicular lymphoma as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy*
 - b. Diffuse Large B-Cell Lymphoma
 - Previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens*
 - c. Chronic Lymphocytic Leukemia
 - Previously untreated and previously treated CLL in combination with fludarabine and cyclophosphamide*
3. Ofatumumab (Arzerra) may be considered medically necessary for:
 - As a single agent or in combination with fludarabine and cyclophosphamide for the treatment of relapsed/refractory CLL*
 - In combination with chlorambucil for the treatment of previously untreated CLL in patients not suitable for treatment with fludarabine*
 - Extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL*
 - The treatment of patients with CLL refractory to fludarabine and alemtuzumab*
4. Obinutuzumab (Gazyva) may be considered medically necessary for:
 - The treatment of previously untreated B-cell CLL, when used in combination with chlorambucil*
 - The treatment of relapsed/refractory B-CLL without del (17p) mutation, as a single agent
 - The treatment of patients with follicular lymphoma who relapsed after or are refractory to a prior rituximab-containing regimen, when used in combination with bendamustine, followed by Gazyva monotherapy*
 - The treatment of adult patients with previously untreated stage II bulky, III, or IV follicular lymphoma, in combination with chemotherapy, followed by Gazyva monotherapy, in patients achieving at least a partial remission*
5. Gemtuzumab Ozogamicin (Mylotarg) may be considered medically necessary for:
 - The treatment of newly-diagnosed CD33-positive acute myeloid leukemia (AML) in adults*
 - The treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older*

Treatment of B-CLL with monoclonal antibody therapy may be considered medically necessary for patients with non-localized disease (i.e., Ann Arbor, stage II-IV).

Use of monoclonal antibodies for non-Hodgkin’s lymphoma and acute myeloid leukemia may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either:

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- In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); **OR**
- In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached.

*Indicates an indication approved by the U.S. Food and Drug Administration

When Monoclonal Antibodies for Non-Hodgkin Lymphoma and Acute Myeloid Leukemia are not covered

1. For conditions other than those listed above.
2. Ofatumumab (Arzerra) is considered investigational for the treatment of malignancies other than B-cell CLL.
3. Obinutuzumab (Gazyva) is considered investigational when used for indications outside of FDA labeling and nationally recognized compendia recommendations with the highest level of evidence.

Monoclonal Antibodies for Non-Hodgkin Lymphoma and Acute Myeloid Leukemia are considered investigational when used for:

1. Non-cancer indications; **OR**
2. When criteria are not met regarding FDA labeling **OR** strong endorsement/support by nationally recognized compendia, as stated under “When Monoclonal Antibodies are Covered.”

Policy Guidelines

Rituximab and rituximab biosimilars (rituximab-abbs, rituximab-arrx, and rituximab-pvvr) are currently FDA-approved for the following oncologic indications:

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent;
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first-line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy;
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy;
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens; and
- In combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL.

Rituxan Hycela is currently FDA-approved for the following oncologic indications:

- Follicular lymphoma
- Diffuse large B-cell lymphoma
- Chronic lymphocytic leukemia

Rituximab

For individuals who have non-Hodgkin lymphoma who receive rituximab alone or combined with chemotherapy, the evidence includes randomized controlled trials (RCTs) and nonrandomized

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comparative studies. Relevant outcomes are overall survival, disease-free survival, change in disease status, and quality of life. Randomized trials have shown that the addition of rituximab to front-line chemotherapy has resulted in improved response rates and survival in follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL). The efficacy of rituximab as monotherapy in relapsed and refractory FL has been shown in multicenter studies. Randomized trials have shown improved progression-free survival (PFS) and overall survival with the use of rituximab as maintenance therapy, both in patients with previously untreated and previously treated FL. One study of DLBCL showed improved PFS and overall survival in patients receiving rituximab-containing regimens, including monotherapy, compared with rituximab-free regimens. Randomized trials have shown that the addition of rituximab to chemotherapy has improved response rates and time-to-treatment failure in newly diagnosed mantle cell lymphoma and improved overall survival in relapsed or refractory disease. Randomized trials have also shown improved PFS and overall survival with the addition of rituximab to chemotherapy in previously untreated chronic lymphocytic leukemia (CLL). One randomized trial showed prolonged PFS in relapsed or refractory CLL, and a phase 2 open-label study showed improved PFS and overall survival. One RCT showed better event-free survival and overall survival in patients with Burkitt lymphoma when combined with chemotherapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome

Ofatumumab (Arzerra)

For individuals who have non-Hodgkin lymphoma who receive ofatumumab alone or combined with chemotherapy, the evidence includes RCTs and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-free survival, change in disease status, and quality of life. Ofatumumab has been shown to improve PFS when used as first-line therapy and to treat relapsed and refractory CLL under certain conditions. Based on a phase 3 RCT (COMPLEMENT 1), ofatumumab improved PFS for first-line therapy in previously untreated CLL in patients not candidates for treatment with fludarabine. In another phase 3 RCT, ofatumumab improved PFS when combined with fludarabine and cyclophosphamide to treat relapsed CLL. Ofatumumab also improved PFS for treatment of CLL refractory to fludarabine based on response rates in CLL treatment-resistant groups. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Obinutuzumab (Gazyva)

For individuals who have non-Hodgkin lymphoma who receive obinutuzumab alone or combined with chemotherapy, the evidence includes RCTs. Relevant outcomes are overall survival, disease-free survival, change in disease status, and quality of life. Obinutuzumab was approved by FDA for the treatment of FL in patients who have relapsed or are refractory to a rituximab-containing regimen and for use in combination with chlorambucil for previously untreated CLL in combination with bendamustine. These indications are based on positive results in phase 3 trials that compared combination therapy to monotherapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Gemtuzumab Ozogamicin (Mylotarg)

Mylotarg is a CD33-directed antibody-drug conjugate indicated for treatment of newly-diagnosed CD33-positive acute myeloid leukemia (AML) in adults and for treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older.

Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy (CMP), “Investigational (Experimental) Services.”

Please refer to CMP “Investigational (Experimental) Services” for a summary of evidence standards from nationally recognized compendia.

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Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: C9399, J0202, J3490, J3590, J9203, J9301, J9302, J9311, J9312, J9999, Q5115, Q5119, S0353, S0354

ICD-10 Codes: C00.0-C49.9, C4A.0-C4A.9, C50.011-C79.9, C7A.00-C7A.8, C7B.00-C7B.8, C80.0-C86.6, C88.2-C96.Z, D00.00-D09.9, Z51.11, Z51.12

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual, 2.03.05, 5/14/09

Senior Medical Director 7/2009

Specialty Matched Consultant Advisory Panel – 5/2010

BCBSA Medical Policy Reference Manual, 2.03.05, 5/13/2010

Specialty Matched Consultant Advisory Panel – 4/2011

BCBSA Medical Policy Reference Manual. 2.03.05, 5/12/11

Medical Director – 8/2011

Specialty Matched Consultant Advisory Panel – 4/2012

BCBSA Medical Policy Reference Manual. 2.03.05, 5/10/2012

Specialty Matched Consultant Advisory Panel 4/2013

BCBSA Medical Policy Reference Manual. 2.03.05, 7/11/2013

Senior Medical Director – 8/2013

Specialty Matched Consultant Advisory Panel – 4/2014

NCCN Clinical Practice Guidelines in Oncology. Version 2.2014. Accessed 4/30/2014 from http://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf

FDA News Release. FDA approves Gazyva for chronic lymphocytic leukemia. Accessed 4/30/2014 from <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm373209.htm>

Senior Medical Director review 5/1/2014

BCBSA Medical Policy Reference Manual. 2.03.05, 7/10/2014

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Specialty Matched Consultant Advisory Panel- 4/2015

BCBSA Medical Policy Reference Manual. 2.03.05, 7/9/2015

Senior Medical Director review 7/2015

Specialty Matched Consultant Advisory Panel- 4/2016

U. S. Food and Drug Administration (FDA). Available at:
http://www.gene.com/download/pdf/gazyva_prescribing.pdf

Medical Director review 4/2016

NCCN Clinical Practice Guidelines in Oncology. <http://www.nccn.org/>

Carton G, de Guibert S, Dilhuydy MS, et al. Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase 1/2 GAUGUIN study. *Blood*. 2014 Oct 2;124(14):2196-202. PMID: 25143487

Medical Director review 9/2016

BCBSA Medical Policy Reference Manual. 2.03.05, 11/10/2016

Medical Director review 12/2016

Specialty Matched Consultant Advisory Panel- 4/2017

Medical Director review 4/2017

U. S. Food and Drug Administration (FDA). Available at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761064s000lbl.pdf

Senior Medical Director review 8/2017

U. S. Food and Drug Administration (FDA). Available at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761060lbl.pdf

Novartis Pharmaceuticals Corporation. Arzerra (ofatumumab) injection, for intravenous use. Prescribing Information. East Hanover, NJ:Novartis; Revised 8/2016. Available at: <https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/arzerra.pdf>. Accessed April 2018.

BCBSA Medical Policy Reference Manual. 2.03.05, 10/12/2017

Specialty Matched Consultant Advisory Panel- 4/2018

BCBSA Medical Policy Reference Manual. 2.03.05, 10/10/2018

Specialty Matched Consultant Advisory Panel- 4/2019

Pfizer Inc. Ruxience (rituximab-pvvr) injection, for intravenous use. Highlights of prescribing information. July 2019. Available at: <http://labeling.pfizer.com/ShowLabeling.aspx?id=12090>. Last accessed October 2019.

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Teva Pharmaceuticals USA, Inc. Truxima (rituximab-abbs) injection, for intravenous use. Highlights of prescribing information. May 2019. Available at: <https://www.truxima.com/globalassets/truxima-dtc/pdfs/truxima-prescribing-information.pdf>. Last accessed October 2019.

BCBSA Medical Policy Reference Manual. 2.03.05, 10/17/2019

Medical Director review 11/2019

Specialty Matched Consultant Advisory Panel- 4/2020

Medical Director review 10/2020

Amgen, Inc. Riabni (rituximab-arrx) injection, for intravenous use. Highlights of prescribing information. December 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761140s0001bl.pdf. Last accessed January 2021.

Medical Director review 1/2021

Policy Implementation/Update Information

For Evidence Based Guideline titled “Monoclonal Antibodies for Non-Hodgkin Lymphoma, including Chronic Lymphocytic and Acute Myeloid Leukemia in the Non-Hematopoietic Stem Cell Transplant Setting”

9/28/09 New evidence based guideline. Reviewed with Senior Medical Director 7/20/09. (btw)

6/22/10 Policy Guideline Number(s) removed (amw)

7/6/2010 Specialty Matched Consultant Advisory Panel review 5/24/2010. No changes to Guideline. References added. (btw)

5/24/11 Specialty Matched Consultant Advisory Panel review 4/27/11. Updated “Description” section. Added the following statement to #3 in the “Evidence-Based Guideline” section; “Note that in June 2010, Pfizer, Inc. announced the voluntary withdrawal of Mylotarg® (gemtuzumab ozogamicin) from the U.S. market. Patients who are currently receiving the drug may continue their planned course of therapy; however, Mylotarg® will not be commercially available to new patients.” References added. (btw)

08/16/11 Updated “Description” section to include information related to Ofatumumab (Arzerra) and to update the Regulatory Status. Added the following statement to the “Evidence Based Guideline” section to indicate; “Rituxan may be appropriate a. for follicular lymphoma: as first-line therapy (as combination therapy or as monotherapy), as second or subsequent therapy (as combination therapy or as monotherapy), as single-agent maintenance therapy (first- or second-line) in patients who achieve a complete or partial response to Rituxan in combination with chemotherapy.” and “Ofatumumab (Arzerra) may be appropriate for the treatment of CLL that is refractory to fludarabine and alemtuzumab.*” Rituximab approved FDA indications added. “Ofatumumab (Arzerra) is not recommended in previously untreated CLL or as maintenance therapy in patients with CLL.” Added to the “Not Recommended” section. References added. Medical Director review 8/6/2011. (btw)

5/15/12 Specialty Matched Consultant Advisory Panel review 4/18/2012 No change to policy intent. (btw)

6/29/12 Reference added. (btw)

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- 5/14/13 Specialty Matched Consultant Advisory Panel review 4/17/2013. Added the following statement to the Description section; “Labeling indications for alemtuzumab are as monotherapy for the treatment of CLL.” Added “and previously treated” to l.e. under Evidence Based Guideline section. (btw)
- 9/10/13 Added the following statement to the When Not Recommended section; “Ofatumumab (Arzerra®) is not recommended for the treatment of malignancies other than B-cell CLL.” Senior Medical Director review 8/29/2013. Reference added. (btw)
- 5/27/14 Specialty Matched Consultant Advisory Panel review 4/29/2014. Added “rituximab may be appropriate for 1st line and subsequent line treatment for all CD20 B cell malignancies including mantle cell lymphoma, marginal zone lymphoma and Burkitt lymphoma.” “Obinatumumab (Gazyva) may be appropriate in combination with chlorambucil as 1st line treatment of chronic lymphocytic leukemia (CLL).” Reference added. (btw)
- 9/30/14 Updated “Description” section. Added “ofatumumab may be appropriate in patients with previously untreated CLL who are not suitable for treatment with fludarabine,” and “obinatumumab may be appropriate in previously untreated B-cell CLL when used in combination with chlorambucil.” Senior Medical Director review 9/2014. Reference added. (lpr)
- 12/30/14 Added HCPCS code J9301 to Billing/Coding section for effective date 1/1/2015. (lpr)
- 5/26/15 Evidence based guideline converted to corporate medical policy. Medical Director review. Specialty matched consultant advisory panel review 4/2015. Removed all references to Gemtuzumab (Mylotarg) since this medication was withdrawn from the market in 2010. Notification given 5/26/15 for effective date 7/28/15. (lpr)

For Corporate Medical Policy Re-titled “Monoclonal Antibodies for Non-Hodgkin Lymphoma and Acute Myeloid Leukemia in the Non-Hematopoietic Stem Cell Transplant Setting”

- 9/1/15 Policy re-titled “Monoclonal Antibodies for Non-Hodgkin Lymphoma and Acute Myeloid Leukemia in the Non-Hematopoietic Stem Cell Transplant Setting.” Under “When Covered” section added medically necessary indication for post-transplant lymphoproliferative disorder for Rituximab. Reference added. Senior medical director review 7/2015. (lpr)
- 12/30/15 Added HCPCS code J0202 to Billing/Coding section effective 1/1/2016. (lpr)
- 5/31/16 Updated Policy Guidelines and Regulatory status sections. Under “When Covered” #3 Obinatumumab (Gazyva™) added a bullet to indicate medical necessity for: “the treatment of follicular lymphoma that has progressed on a prior rituximab regimen when used in combination with bendamustine followed by Gazyva monotherapy *”. Under “When Not Covered” clarified bullet #4 “Obinatumumab (Gazyva™) is considered investigational when used for indications outside of FDA labeling and nationally recognized compendia recommendations with the highest level of evidence.” Specialty Matched Consultant Advisory Panel review 4/27/2016. Reference added. (lpr)
- 12/30/16 Added HCPCS codes J9302, S0353, S0354 and deleted J9010, J9300 in “Billing/Coding” section. Also added ICD-10 diagnoses codes to the “Billing/Coding” section. Medical Director review 9/2016. Revisions under “When Covered” (WC) section: Bullet c. added “CD positive”, Bullet g. added “Castleman’s disease.”, Bullet f. added Burkitt lymphoma. Also in WC section #2 Ofatumumab (Arzerra): removed statements: “the treatment of CLL that is refractory to fludarabine and alemtuzumab * and previously untreated CLL in patients

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not suitable for treatment with fludarabine. **” and added the following statements: “As a single agent or in combination with fludarabine and cyclophosphamide for the treatment of relapsed/refractory CLL in combination with chlorambucil previously untreated CLL in patients not suitable for treatment with fludarabine and for extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL.” Gemtuzumab and alemtuzumab removed from policy due to withdrawal from market. Added covered indication for Burkitt lymphoma under Rituximab. Added covered indication for follicular lymphoma under Obinutuzumab. Updated Regulatory status, Description section and Policy Guidelines sections. Reference added. Medical Director review 12/2016. Notification given 12/30/16 for effective date 4/1/17. (lpr)

- 5/26/17 Specialty Matched Consultant Advisory Panel review 4/26/2017. Added the following statement to “When Covered” section: “Use of Monoclonal Antibodies for Nonhodgkin Lymphoma and Acute Myeloid Leukemia may be considered medically necessary for clinical indications not listed above when prescribed for the treatment of cancer either: In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); OR In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached”. Added the following statements under “Policy Guidelines” section: 1) Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy, Investigational (Experimental) Services.” 2) Please refer to CMP “Investigational (Experimental) Services” for a summary of evidence standards from nationally recognized compendia. Medical director review 4/2017. No change to policy statement. (lpr)
- 9/15/17 Updated Policy Guidelines section. Under “When Covered” section: added medically necessary coverage indications for Rituxan Hycela. Reference added. Senior Medical Director review 8/2017. Pharmacy review 8/2017. (lpr)
- 12/29/17 Updated the Description and Policy Guidelines sections. Added the following statement to the “When Covered” section: Gemtuzumab Ozogamicin (Mylotarg™) may be considered medically necessary for: the treatment of newly-diagnosed CD33-positive acute myeloid leukemia (AML) in adults; the treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients 2 years and older. Added HCPCS code J9203 to Billing/Coding section. **Policy noticed 12/29/17 for effective date 3/29/18.** Reference added. (lpr)
- 5/11/18 Specialty Matched Consultant Advisory Panel review 4/2018. Under “When Not Covered” section, removed the following statement from when ofatumumab (Arzerra) is considered investigational: “as maintenance therapy in patients with CLL” to coincide with indication listed in “When Covered” section. References added. Added HCPCS code C9467 to Billing/Coding section. (krc)
- 12/31/18 Added HCPCS code J9311 to Billing/Coding section and deleted code C9467 effective 1/1/19. (krc)
- 1/15/19 Added HCPCS code J9312 to Billing/Coding section and deleted code J9310 effective 1/1/19. Reference added. (krc)
- 4/30/19 Under “When Covered” for Ofatumumab (Arzerra), added the following indication: “for the treatment of patients with CLL refractory to fludarabine and alemtuzumab”; and restructured existing indications for clarity with no change to policy intent. Added the following

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indication under “When Covered” for Obinutuzumab (Gazyva): “the treatment of adult patients with previously untreated stage II bulky, III, or IV follicular lymphoma, in combination with chemotherapy, followed by Gazyva monotherapy, in patients achieving at least a partial remission.” Specialty Matched Consultant Advisory Panel review 4/17/2019. (krc)

- 11/12/19 Under “When Covered” for Rituxan (rituximab), added Truxima (rituximab-abbs) and Ruxience (rituximab-pvvr) biosimilars with same indications as Rituxan (rituximab). Updated policy statements for rituximab and rituximab biosimilars to provide clarification and consistency with FDA labeling where appropriate, with no change to policy intent. Added HCPCS codes C9399, J3490, J3590, J9999, and Q5115 to Billing/Coding section. References added. Medical Director review 11/2019. **Policy notification given 11/12/2019 for effective date 1/14/2020.** (krc)
- 1/14/20 Updated policy statements for Gazyva to provide clarification and consistency with FDA labeling where appropriate, with no change to policy intent. Added regulatory information for Rituxan Hycela within “Description” section for clarity. Reference added. (krc)
- 6/9/20 Specialty Matched Consultant Advisory Panel review 4/15/2020. No change to policy statements. (krc)
- 6/30/20 Added HCPCS code Q5119 to Billing/Coding section effective 7/1/2020. (krc)
- 10/27/20 Added following requirements to “When Covered” section: “If the request is for rituximab (Rituxan) or non-preferred rituximab biosimilars, then both of the following criteria are met: patient has a documented serious adverse event that required medical intervention to both preferred rituximab biosimilar products [rituximab-abbs (Truxima), rituximab-pvvr (Ruxience)] that is not anticipated with the requested product AND prescriber has completed and submitted an FDA MedWatch Adverse Event Reporting Form.” Minor typographical and formatting changes made throughout for clarity. Medical Director review 10/2020. **Policy notification given 10/27/2020 for effective date 1/1/2021.**
- 1/12/21 Under “When Covered” for Rituxan (rituximab), added Riabni (rituximab-arrx) biosimilar with same indications and coverage criteria as Rituxan (rituximab). Reference added. Medical Director review 1/2021. **Policy notification given 1/12/2021 for effective date 4/1/2021.** (krc)

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