

Rituximab

DESCRIPTION

Rituximab is a genetically engineered monoclonal antibody which binds specifically to the human CD20 antigen. The CD20 antigen is expressed on greater than 90% of B-cell non-Hodgkin's lymphomas and is found on the abnormal B-cells of chronic lymphocytic leukemia (CLL). Additionally, B-cells expressing the CD20 antigen are believed to play a role in the pathogenesis of rheumatoid arthritis.

In binding with the CD-20 antigen on B lymphocytes, rituximab likely recruits immune effector functions to mediate B-cell lysis, possibly through complement-dependent cytotoxicity (CDC) or antibody-dependent cell mediated cytotoxicity (ADCC). Rituximab has also been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line.

POLICY

- Rituximab for the treatment of the following is considered **medically necessary** if the medical appropriateness criteria are met: **(See Medical Appropriateness below.)**
 - Acute lymphoblastic leukemia (ALL)
 - Autoimmune Hemolytic Anemia (AIHA)
 - Central nervous system cancers
 - Chronic graft-versus-host disease
 - Chronic lymphocytic leukemia (CLL) / Small lymphocytic lymphoma (SLL)
 - Hodgkin's lymphoma
 - Idiopathic/immune thrombocytopenic purpura (ITP)
 - Idiopathic inflammatory myopathy (e.g., myositis, dermatomyositis, polymyositis)
 - Management of Immunotherapy-Related Toxicities
 - Neuromyelitis optica / neuromyelitis optica spectrum disease (NMO/NMOSD)
 - Non-Hodgkin's lymphomas (NHL), including, but not limited to:
 - AIDS-related B-Cell Lymphoma
 - Burkitt Lymphoma
 - Castleman's Disease
 - Diffuse Large B-Cell Lymphoma
 - Gastric & Non-gastric Malt Lymphoma
 - Hairy Cell Leukemia
 - **High Grade B-Cell Lymphoma**
 - **Histologic transformation of Marginal Zone Lymphoma to Diffuse Large B-Cell Lymphoma**
 - Low-grade or Follicular Lymphoma
 - Lymphoma following solid organ transplant or allogeneic hematopoietic stem cell transplantation
 - Mantle Cell Lymphoma
 - Nodal & Splenic Marginal Zone Lymphoma
 - Marginal Zone Lymphoma
 - Post-transplant lymphoproliferative disorder (PTLD)
 - Primary Cutaneous B-Cell Lymphomas
 - Pemphigus vulgaris
 - Rheumatoid arthritis (RA)
 - Thrombotic Thrombocytopenic Purpura (TTP)
 - Waldenström's macroglobulinemia / lymphoplasmacytic lymphoma
 - Wegener's granulomatosis (WG) (Granulomatosis with polyangiitis [GPA]) / microscopic polyangiitis (MPA)
- Rituximab for the treatment of other conditions/diseases is considered **investigational**.

MEDICAL APPROPRIATENESS

The proposal is to add text/statements in red and to delete text/statements with strikethrough:

INITIAL APPROVAL

- Rituximab is considered **medically appropriate** if **ALL** of the following criteria are met:
 - Individual must be screened for HBV infection (i.e., HBsAg and anti-HBc) prior to initiating therapy
 - **For ANY ONE of the following:**
 - Oncology indication the individual must be CD20-positive
 - **Non-oncology indication the individual is not on concurrent treatment with another TNF-inhibitor, biologic response modifier or other non-biologic agent (e.g., apremilast, tofacitinib, baricitinib)**
 - Diagnosis of **ANY ONE** of the following:
 - Acute lymphocytic/lymphoblastic leukemia (ALL) if individual is 15 years of age or older and **ANY ONE** of the following:
 - Treatment is for Induction / Consolidation with **ALL** of the following:
 - Disease is Philadelphia chromosome-negative (Ph-)
 - Used in combination with an anthracycline, cyclophosphamide and vincristine based regimen
 - Treatment is Relapsed / Refractory disease if **ALL** of the following:
 - Used as a component of MOpAD regimen (methotrexate, vincristine, pegaspargase, dexamethasone)
 - Disease is Philadelphia chromosome-negative (Ph-) or Philadelphia chromosome-positive (Ph+) and refractory to tyrosine kinase inhibitors (e.g.; ~~imatinib~~, imatinib, bosutinib, ponatinib, nilotinib, etc.)
 - Autoimmune Hemolytic Anemia (AIHA) if **ANY ONE** of the following:
 - Individual has warm-reactive disease refractory to or dependent on glucocorticoids
 - Individual has cold agglutinin disease with symptomatic anemia, transfusion-dependence, and/or disabling circulatory symptoms
 - Central nervous system cancer of **ANY ONE** of the following:
 - Leptomeningeal metastases from lymphomas and rituximab will be administered intrathecally
 - Primary CNS lymphoma if used intrathecally with positive disease on lumbar puncture or spinal MRI as **ANY ONE** of the following:
 - In combination with methotrexate-containing regimen as a component of induction therapy and/or consolidation therapy with a complete response (CR) or a complete response unconfirmed (CRu) to induction therapy
 - Relapsed or refractory disease and will receive rituximab as a single agent or in combination with temozolomide or high-dose methotrexate
 - Chronic graft-versus-host disease (cGVHD) if **ALL** of the following:
 - Post allogeneic stem cell transplant (generally 3 or more months)
 - Failed one or more previous lines of systemic therapy for the treatment of cGVHD (e.g., corticosteroids or immunosuppressants such as cyclosporine)
 - Tried and had an inadequate response, contraindication, or intolerance to at least a three (3) month trial of ibrutinib
 - Chronic lymphocytic leukemia (CLL) / Small lymphocytic lymphoma (SLL) used as **ANY ONE** of the following:
 - In combination with fludarabine and cyclophosphamide (FC)
 - First-line therapy in combination with chlorambucil or bendamustine, or alemtuzumab in individuals without del(17p)/TP53 mutation
 - First line therapy in combination with fludarabine in individuals without del(17p)/TP53 and del(11q) mutations
 - First line therapy in combination with high-dose methylprednisolone ~~and~~ **or** alemtuzumab with del(17p)/TP53 mutations
 - Relapsed or refractory disease in combination with **ANY ONE** of the following:



- Venetoclax or idelalisib or lenalidomide or high-dose methylprednisolone
- Chlorambucil without del(17p) mutations
- **Without del (17p)/TP53 mutations in combination with ANY ONE of the following:**
 - Alemtuzumab, high-dose methylprednisolone, or lenalidomide
 - As a component of FCR (fludarabine, cyclophosphamide, and rituximab) or PCR (pentostatin, cyclophosphamide, and rituximab)
- **With del(17p)/TP53 mutations in combination with ANY ONE of the following:**
 - Idelalisib or venetoclax
 - Alemtuzumab, lenalidomide, or high-dose methylprednisolone
- **First line therapy for histologic (Richter's) transformation to diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, and vincristine based OR oxaliplatin, fludarabine, cytarabine based regimen.**
- Hodgkin lymphoma that is nodular lymphocyte-predominant disease
- Idiopathic inflammatory myopathy (e.g., dermatomyositis, myositis, polymyositis, inclusion body myositis) if intolerant to or inadequate response to prior treatment with **ALL** of the following:
 - Glucocorticoids
 - Minimum of one other immunosuppressive or immunomodulatory agent (e.g. azathioprine, methotrexate, mycophenolate, mofetil, cyclosporine, tacrolimus, cyclophosphamide, leflunomide or IVIg)
- Management of Immunotherapy-Related Toxicities if individual is/has **ALL** of the following:
 - Received therapy with an immune checkpoint inhibitor (e.g. cemiplimab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, ipilimumab, etc.)
 - Diagnosis of non-viral encephalitis related to immunotherapy treatment
 - Autoimmune-encephalopathy-antibody positive
 - Refractory to methylprednisolone and/or IV immunoglobulin (IVIg)
- Neuromyelitis optica / neuromyelitis optica spectrum disease (NMO/NMOSD) for **ANY ONE** of the following:
 - Treatment-naïve individual with high disease activity as first-line therapy
 - Individual who relapsed or was refractory to one or more prior treatment including previous immunosuppressive therapy (e.g., azathioprine)
- Non-Hodgkin lymphoma (NHL) including but not limited to, the following:
 - AIDS-related B-Cell Lymphoma if **ALL** of the following:
 - Used **as a single agent** or in combination with other chemotherapy
 - Disease is related to Burkitt lymphoma or diffuse large B-cell Lymphoma
 - Burkitt Lymphoma in combination with other chemotherapy
 - Castleman's Disease if disease is **ANY ONE** of the following:
 - Multicentric disease
 - Unicentric disease if used for **ANY ONE** of the following:
 - Second-line therapy for relapsed or refractory disease
 - Individual with symptoms after resection of unresectable disease
 - Diffuse Large B-Cell Lymphoma
 - Gastric & Non-Gastric MALT Lymphoma
 - Hairy Cell Leukemia used for relapsed or refractory disease or less than complete response (CR) to initial therapy
 - **High Grade B-Cell Lymphoma**
 - **Histologic transformation of Marginal Zone Lymphoma to Diffuse Large B-Cell Lymphoma**
 - Low-grade or Follicular Lymphoma
 - disease after achieving a complete response (CR) on first-line therapy
 - Mantle Cell Lymphoma
 - Nodal & Splenic Marginal Zone Lymphoma

- Post-transplant lymphoproliferative disorder (PTLD) if lymphoma following solid organ transplant or allogeneic hematopoietic stem cell transplantation used as **ANY ONE** of the following:
 - First-line or subsequent therapy for monomorphic or polymorphic disease
 - **Single agent** maintenance therapy for polymorphic **disease after achieving a complete response on first-line therapy**
- Primary Cutaneous B-Cell Lymphomas used for generalized (skin only), marginal zone or follicle center disease
- Pemphigus vulgaris if **ALL** of the following:
 - Individual is 18 years of age or older
 - Diagnosis by confirmation of **ANY ONE** of the following:
 - Clinical features of the appearance of lesions, erosions and/or blisters, Nikolsky sign (induction of blistering via mechanical pressure at the edge of a blister or on normal skin), characteristic scarring and lesion distribution
 - Histopathologic confirmation by skin/mucous membrane biopsy
 - Presence of autoantibodies as detected by direct or indirect immunofluorescence
 - Moderate to severe disease as assessed utilizing an objective measure/tool (i.e. PDAI, PSS, ABSIS)
 - Individual is on combination glucocorticoid therapy
 - Other causes of blistering or erosive skin and mucous membrane diseases have been ruled out
- Rheumatoid arthritis if **ALL** of the following:
 - Individual is 18 years of age or older
 - Disease is moderately- to severely-active
 - Used in combination with methotrexate (MTX) unless individual has a contraindication or intolerance
 - Individual tried and failed a minimum 3 month trial with ONE oral disease modifying anti-rheumatic agent (DMARD) (e.g., methotrexate, azathioprine, auranofin, hydroxychloroquine, penicillamine, sulfasalazine, leflunomide, etc.)
 - Previous failure/inadequate response with one or more preferred tumor necrosis factor (TNF) antagonist therapies, at least one of which should be a self-injectable
 - Individual has NOT had treatment with rituximab in the previous 4 months
 - Physician has assessed baseline disease severity utilizing an objective measure/tool
- Thrombocytopenic purpura if **ALL** of the following:
 - Individual previously failed or has a contraindication or intolerance to therapy with corticosteroids
 - Increased risk for bleeding as indicated by platelet count (within the previous 28 days) less than $30 \times 10^9/L$ ($30,000/mm^3$)
 - Diagnosis is **ANY ONE** of the following:
 - Primary thrombocytopenia
 - Idiopathic (Immune) thrombocytopenia purpura (ITP)
 - Evan's syndrome
 - Congenital and hereditary thrombocytopenic purpura
 - Thrombotic thrombocytopenic purpura in patients with ADAMTS13-deficiency
- Waldenström's macroglobulinemia / lymphoplasmacytic lymphoma
- Wegener's granulomatosis (WG) (Granulomatosis with polyangiitis [GPA]) and Microscopic Polyangiitis (MPA) if **ALL** of the following:
 - Individual is 18 years of age or older
 - Treatment is in combination with glucocorticoids (e.g., prednisone, methylprednisolone, etc.)

RENEWAL CRITERIA

- Rituximab is considered **medically appropriate** for renewal if **ALL** of the following criteria are met:
 - Individual continues to meet initial approval criteria



- Absence of unacceptable toxicity from the drug such as severe infusion-related reactions, tumor lysis syndrome (TLS), severe mucocutaneous reactions, progressive multifocal leukoencephalopathy (PML), ~~viral~~ hepatitis B virus reactivation, serious bacterial, fungal, or viral infections, cardiac arrhythmias, renal toxicity, bowel obstruction or perforation
- Diagnosis of **ANY ONE** of the following:
 - Oncology applications with **ALL** of the following:
 - ~~Disease response with stabilization of disease or decrease in size of tumor or tumor spread~~ **Disease response with treatment as defined by stabilization of disease or decrease** Tumor response with stabilization of disease or decrease in size of tumor or tumor spread
 - Individual has not exceeded dosing limits
 - Non-oncology applications of **ANY ONE** of the following:
 - Autoimmune hemolytic anemia (AIHA) with disease response as indicated by improvement in anemia signs and symptoms (e.g., dyspnea, fatigue, etc.) as well as: improvement in laboratory values (Hb/Hct), reduced transfusion needs, and/or reduced glucocorticoid use
 - Chronic graft-versus-host disease (cGVHD) with disease response as indicated by improvement in patient-reported symptoms or clinician assessments (e.g., manifestations of disease to the skin, oral cavity, musculoskeletal system, etc.)
 - Idiopathic inflammatory myopathy with disease response as indicated by improvement in signs and symptoms of condition compared to baseline
 - Neuromyelitis optica / neuromyelitis optica spectrum disease (NMO/NMOSD) with disease response as indicated by improvement in signs and symptoms of condition compared to baseline
 - Pemphigus vulgaris, Wegener's granulomatosis (WG) (Granulomatosis with polyangiitis [GPA]) and Microscopic Polyangiitis (MPA) with disease response as indicated by disease control and improvement in signs and symptoms of condition compared to baseline and a decreased frequency in the occurrence of major relapses (defined by the reappearance of clinical and/or laboratory signs of vasculitis activity that could lead to organ failure or damage, or could be life threatening)
 - Rheumatoid arthritis (RA) with disease response as indicated by improvement in signs and compared to baseline such as the number of tender and swollen joint counts, **reduction of C-reactive protein, improvement of patient global assessment** and/or an improvement on a disease activity scoring tool [e.g. an improvement on a composite scoring index such as Disease Activity Score-28 (DAS28) of 1.2 points or more or a ≥20% improvement on the American College of Rheumatology-20 (ACR20) criteria] and dose escalation (up to the maximum dose and frequency specified below) may occur upon clinical review on a case by case basis provided that the patient has:
 - Shown an initial response to therapy
 - Received a minimum of one maintenance dose at the dose and interval specified below
 - Responded to therapy with subsequent loss of response
 - Thrombocytopenic purpura with disease response as indicated by the achievement and maintenance of a platelet count of at least 50 × 10⁹/L as necessary to reduce the risk for bleeding
 - Thrombotic thrombocytopenic purpura (TTP) with disease response as indicated by an increase in ADAMTS13 activity with a reduction in thrombotic risk
 - Wegener's granulomatosis (Granulomatosis with Polyangiitis) (GPA) and Microscopic polyangiitis (MPA) - Disease response as indicated by improvement in signs and symptoms of condition compared to baseline
 - All others as indicated by improvement in signs and symptoms of condition compared to baseline

INDICATION(S)	DOSAGE & ADMINISTRATION
CLL/SLL	<p>Initial therapy - 375 mg/m² weekly x 8 doses; OR 375 mg/m² cycle 1, then 500 mg/m² every 28 days cycles 2-6 (6 total doses)</p> <p>Renewal therapy - 375 mg/m² once weekly for 4 doses per 6 month period; OR 375mg/ m² every 8 weeks</p>



NHL, PTL, Waldenström's, Castleman's or HL	<p>Initial therapy - 375 mg/m² once weekly for 4 - 8 doses in a 6 month period</p> <p>Renewal therapy - 375 mg/m² once weekly for 4 doses per 6 month period; OR 375mg/ m² every 8 weeks</p>
CNS Lymphoma	<p>Intravenous Initial: 375 mg/m² once weekly for 4 - 8 doses in a 6 month period Renewal Therapy:375 mg/m² once weekly for 4 doses per 6 month period; OR 375 mg/ m² every 8 weeks</p> <p>Intrathecal/Intraventricular 10-40 mg weekly to every 3 weeks</p>
ALL	375 mg/m ² once weekly for 4 - 8 doses in a 6 month period
RA	1,000 mg on days 1 and 15, repeated up to every 16 weeks
Pemphigus Vulgaris	<p>Initiation Administer 1,000 mg on days 1 and 15 in combination with tapering doses of glucocorticoids</p> <p>Maintenance Administer 500 mg at month 12 and repeat every 6 months thereafter or based on clinical evaluation.</p> <p>Relapse Administer 1000 mg upon relapse, resumption of glucocorticoids may be considered. <i>*Subsequent infusions (maintenance and relapse) should be no sooner than 16 weeks after the previous infusion.</i></p>
GPA (WG), MPA	<p>Induction 375 mg/m² weekly x 4 doses, initially</p> <p>Maintenance Administer 1,000 mg (as 2 x 500mg doses) for two doses separated by two weeks, then followed by 500mg every 6 months thereafter based on clinical evaluation. <i>*Initial MAINTENANCE infusions should be no sooner than 16 weeks and no later than 24 weeks after the previous infusion if Rituxan was used for initial induction therapy.</i> <i>*Initial MAINTENANCE infusions should be initiated within 4 weeks following disease control when initial induction occurred with other standard of care immunosuppressants.</i></p>
AIHA, Thrombocytopenia or Immunotherapy Toxicity Treatment	375 mg/m ² weekly x 4 doses in a 6 month period
cGVHD	375 mg/m ² weekly x 4 doses, then 375 mg/m ² monthly x 4 months

LENGTH OF AUTHORIZATION

Coverage will be provided for 6 months (12 months initially for pemphigus vulgaris) and may be renewed unless otherwise specified.

Maintenance therapy for oncology indications (excluding ALL) may be renewed for up to a maximum of 2 years.

Acute lymphoblastic leukemia (ALL) may not be renewed.

Relapse therapy for pemphigus vulgaris must be at least 16 weeks past a prior infusion

Refer to **DOSAGE LIMITS** below

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the Medical Policy and a health plan, the express terms of the health plan will govern.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

SOURCES

Pemphigus & Pemphigoid Foundation. (2017) *For Medical Professionals - Diagnostic Testing*. Retrieved September 17, 2018 from <http://www.pemphigus.org/research/clinically-speaking/diagnostic-testing/>.

Joly, B. S., Coppo, P., Veyradier, A. (2017, May). Thrombotic thrombocytopenic purpura. *Blood*, 129 (21), 2836-2846.

Lexi-Comp Online. (2019, February). AHFS DI. *Rituximab*. Retrieved March 29, 2019 from Lexi-Comp Online with AHFS.

MICROMEDEX Healthcare Series. Drugdex Drug Evaluations. (2019, February). *Rituximab*. Retrieved March 29, 2019 from MICROMEDEX Healthcare Series.

Moghadam-Kia, S., Aggarwal, S., Oddis, C. V. (2015). Treatment of inflammatory myopathy: emerging therapies and therapeutic targets. *Expert Review of Clinical Immunology*. (11)11, 1265-1275.

National Comprehensive Cancer Network. (2019). NCCN Drugs & Biologics Compendium®. *Rituximab*. Retrieved March 29, 2019 from the National Comprehensive Cancer Network.

Oddis, C. V., Reed, A. M., Aggarwal, R., Rider, L. G., Ascherman, D. P., Levesque, M. C., et al. (2013, February). Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: A randomized, placebo-phase trial. *Arthritis Rheumatology*, 65 (2), 314-324.



BlueCross BlueShield
of Tennessee

Policy

Medical Policy Manual

Draft Revised Policy: Do Not Implement

Trebst, C., Jarius, S., Berthele, A., Paul, F., Schippling, S., Wildemann, B., et al. (2013). Update on the diagnosis and treatment of neuromyelitis optica: Recommendations of the Neuromyelitis Optica Study Group (NEMOS). *Journal of Neurology*. (2014) 261, 1-16.

U. S. Food and Drug Administration. (2019, January). Center for Drug Evaluation and Research. *Rituxan® (rituximab) injection for intravenous use*. Retrieved March 29, 2019 from https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103705s5454lbl.pdf.

EFFECTIVE DATE

ID_MRx