rituximab Products

Policy # 00218
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

rituximab (Rituxan®), rituximab-abbs (Truxima®), rituximab-pvvr (Ruxience™), rituximab-arrx (Riabni™)

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of rituximab (Rituxan®)‡, rituximab-abbs (Truxima®)‡, rituximab-pvvr (Ruxience™)‡, or rituximab-arrx (Riabni™)‡ to be **eligible for coverage**** when patient selection criteria are met.

Patient Selection Criteria

Coverage eligibility for the use of rituximab (Rituxan), rituximab-abbs (Truxima), rituximab-pvvr (Ruxience), or rituximab-arrx (Riabni) will be considered when the following criteria are met:

- Patient has a diagnosis of B-cell non-Hodgkin's lymphoma (including follicular lymphoma, marginal zone lymphomas, diffuse large B-cell lymphoma, symptomatic Waldenstrom macroglobulinemia, mantle cell lymphoma, and Burkitt lymphoma); OR
- Patient has a diagnosis of chronic lymphocytic leukemia; OR
- Patient has a diagnosis of B-cell acute lymphoblastic leukemia/lymphoblastic lymphoma (ALL/LBL) that is CD20-positive; OR
- Patient has a diagnosis of hairy cell leukemia (HCL); AND
    - Disease is refractory or relapsed (i.e., lack of response to purine analogs or intolerance to purine analogs); OR
- Patient has a diagnosis of thrombotic thrombocytopenic purpura; AND

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- Disease is refractory or relapsed (i.e., lack of response to plasma exchange therapy and glucocorticoids); OR
- Patient has a diagnosis of chronic immune thrombocytopenia (ITP); AND
  - Patient has tried and failed glucocorticoids; OR
- Patient has a diagnosis of granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) or microscopic polyangiitis (MPA); AND
  - Patient is ≥ 2 years of age; AND
  - Requested drug will be used in combination with corticosteroids; OR
- Patient has a diagnosis of rheumatoid arthritis; AND
  - Patient is 18 years or older; AND
  - Patient has failed treatment with one or more tumor necrosis factor (TNF) antagonist therapies (e.g. Enbrel®)‡ AND
  - Requested drug will be used in combination with methotrexate; OR
- Patient has a diagnosis of warm autoimmune hemolytic anemia; AND
  - Disease is refractory to adequate dose and duration of systemic corticosteroid treatment; OR
  - Patient is corticosteroid-dependent (e.g., patient requires high doses of glucocorticoids to maintain response or patient requires maintenance corticosteroids for longer than 3 months); OR
- Patient has a diagnosis of cold agglutination syndrome; OR
- Patient has a diagnosis of multicentric Castleman disease; OR
- Patient has a diagnosis of neuromyelitis optica; AND
  - Patient has tried and failed ONE other immunosuppressant (e.g. azathioprine or mycophenolate); OR
- Patient has a diagnosis of lupus nephritis; AND
  - Disease is refractory to standard first-line treatment (e.g. hydroxychloroquine, chloroquine, corticosteroids, azathioprine, methotrexate, mycophenolate); AND
  - Requested drug will be used as add-on therapy to at least ONE additional treatment (e.g. corticosteroid, cyclophosphamide, or mycophenolate); OR
- Patient has a diagnosis of chronic graft versus host disease; AND
  - Disease is refractory to adequate dose and duration of systemic corticosteroid treatment course; OR

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- Patient has a diagnosis of pemphigus disease (i.e., pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus) or has pemphigoid disease refractory to adequate dose and duration of systemic corticosteroid treatment course.; OR
- Patient has a diagnosis of idiopathic membranous nephropathy; AND
    - Patient has tried and failed an adequate trial of ONE of the following treatment options:
        - Cytotoxic agent (such as cyclophosphamide) in combination with systemic corticosteroids; OR
        - Calcineurin inhibitor (such as tacrolimus); OR
- Patient has a diagnosis of autoimmune encephalitis; OR
- Patient has a diagnosis of hepatitis C virus-associated cryoglobulinemic vasculitis; AND
    - Disease is active and resistant to antiviral drugs; OR
    - Cryoglobulinemia is severe or life threatening; OR
- Patient has a diagnosis of multiple sclerosis and has been previously stabilized on rituximab; OR
- Patient has a diagnosis of myasthenia gravis that is positive for muscle-specific tyrosine kinase (MuSK) antibodies; OR
- Patient has a diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) that is refractory to treatment with glucocorticoids, intravenous immune globulin, or plasma exchange; AND
- If the requested drug is rituximab-abbs (Truxima) or rituximab-arrx (Riabni), patient has tried and failed (e.g., intolerance or inadequate response) BOTH rituximab (Rituxan) AND rituximab-pvvr (Ruxience) for at least TWO months EACH unless there is clinical evidence or patient history that suggests the use of these products will be ineffective or cause an adverse reaction to the patient.
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of rituximab-abbs (Truxima) or rixumab-arrx (Riabni) when the patient has not tried and failed BOTH rituximab (Rituxan) AND rituximab-pvvr (Ruxience) to be **not medically necessary.****

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of rituximab (Rituxan), rituximab-abbs (Truxima), rituximab-pvvr (Ruxience), or rituximab-arrx (Riabni) when patient selection criteria are not met to be **investigational.***

Based on review of available data, the Company considers the use of rituximab (Rituxan), rituximab-abbs (Truxima), rituximab-pvvr (Ruxience), or rituximab-arrx (Riabni) for non-FDA approved indications, including but not limited to the following, to be **investigational.***

- Systemic lupus erythematosus (SLE)
- Multiple sclerosis (new starts)
- Mixed connective tissue disease
- Prophylaxis of graft-versus-host disease
- Induction of immunosuppressive therapy for kidney transplantation
- Treatment of antibody-mediated rejection in solid organ transplant recipients or after pancreatic islet transplantation
- Myasthenia gravis that is NOT MuSK positive
- Minimal change disease.

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rituximab and hyaluronidase, human (Rituxan Hycela™)

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- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of rituximab and hyaluronidase, human (Rituxan Hycela™)‡ to be **eligible for coverage**** when patient selection criteria are met.

Patient Selection Criteria

Coverage eligibility for the use of rituximab and hyaluronidase, human (Rituxan Hycela) will be considered when the following criteria are met:

- Patient has received at least 1 full dose of IV rituximab; AND
    - Patient has a diagnosis of follicular lymphoma; OR
    - Patient has a diagnosis of diffuse large B cell lymphoma; OR
    - Patient has a diagnosis of chronic lymphocytic leukemia.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of rituximab and hyaluronidase, human (Rituxan Hycela) when the patient has not had at least 1 full dose of IV rituximab or when requested for non-FDA approved indications to be **investigational.***

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Background/Overview

Rituximab targets B-cells that have CD20 on their surface (including pre-B cells through mature B-cells; but not stem cells or plasma cells) by several effector mechanisms and is used to decrease the number of B cells in disease states resulting from excessive immune response. These include several types of lymphoma as well as several autoimmune diseases that are thought to be B-cell mediated.

Rituximab is available in two formulations with different administration requirements. Rituxan and its biosimilars, Truxima, Ruxience, and Riabni, are approved for intravenous administration at a rate of 50-400 mg/hr. Rituxan Hycela is a combination of rituximab and hyaluronidase, an endoglycosidase used to increase the dispersion and absorption of rituximab and allowing it to be administered subcutaneously. However, Rituxan Hycela is only approved after the patient has received at least 1 full dose of an intravenous rituximab product.

Both formulations contain black box warnings regarding fatal infusion reactions within 24 hours of infusion, hepatitis B virus reactivation, and progressive multifocal leukoencephalopathy. Approximately 80% of fatal infusion reactions occurred with the first infusion. The intravenous products carry an additional warning for severe mucocutaneous reactions. All black box warnings are potentially fatal.

Lymphoma is a cancer that begins in cells of the immune system. There are two basic categories of lymphomas. One kind is Hodgkin's lymphoma, which is marked by the presence of a type of cell called the Reed-Sternberg cell. The other category is Non-Hodgkin’s Lymphoma (NHL), which includes a large, diverse group of cancers of immune system cells. NHL can be further divided into cancers that have an indolent (slow-growing) course and those that have an aggressive (fast-growing) course. These subtypes behave and respond to treatment differently. Both Hodgkin's and NHL can occur in children and adults, and prognosis and treatment depend on the stage and the type of cancer. Chronic lymphocytic leukemia is a cancer of the white blood cells which causes a slow increase in the number of B lymphocytes in the bone marrow. The cancerous cells spread from the bone marrow to the blood and can affect the lymph nodes and other organs.

Non-Hodgkin's Lymphoma (NHL) includes follicular lymphoma, diffuse large B cell lymphoma, mantle cell lymphoma, Burkitt lymphoma, marginal zone lymphomas, and Waldenstrom macroglobulinemia. Non-Hodgkin's lymphoma begins when a lymphocyte (a B-cell or T-cell)

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becomes abnormal and usually starts in a B-cell in a lymph node. Although NHL can occur in young people, the chance of developing this disease increases with age. Most people with non-Hodgkin's lymphoma are older than 60.

Hairy Cell Leukemia (HCL) is a rare type of indolent B-cell leukemia that comprises about 2% of all lymphoid leukemias. Leukemic cells typically infiltrate the bone marrow and spleen and may also be found in the liver and lymph nodes. Clinically, HCL is characterized by symptoms of fatigue and weakness, and most patients will present with splenomegaly (symptomatic or asymptomatic) and/or hepatomegaly, pancytopenia, and uncommonly peripheral lymphadenopathy. In addition, patients may also present with recurrent opportunistic infections.

Waldenstrom macroglobulinemia is one type of non-Hodgkin's lymphoma and is associated with the overproduction of IgM antibodies. It is also known as lymphoplasmacytic lymphoma. Because there is no available cure and side effects of treatment are potentially dangerous, the condition should only be treated if patients are symptomatic. Symptoms warranting initiation of treatment include recurrent fever, night sweats, weight loss, fatigue, hyperviscosity, symptomatic or bulky lymphadenopathy, symptomatic hepatomegaly or splenomegaly, symptomatic organomegaly and/or organ or tissue infiltration, or peripheral neuropathy.

Thrombocytopenic Purpura can be divided into two types, idiopathic (or immune) and thrombotic. Idiopathic thrombocytopenic purpura (ITP) is an acquired autoimmune disorder with no known cause in which the immune system destroys the body's platelets and can impair platelet production. Corticosteroids, intravenous immunoglobulins (IVIG), or anti-Rho(D) immunoglobulin are standard initial treatments for ITP, but relapses are common within the first year, often requiring splenectomy. Rituximab may be used to delay or avoid splenectomy.

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening condition characterized by microvascular thrombosis, thrombocytopenia, and microangiopathic hemolytic anemia leading to end-organ ischemia and infarction (commonly brain, heart, kidneys). TTP is due to an acquired or congenital deficiency of the von Willebrand factor-cleaving protease, ADAMTS13. When ADAMTS13 is absent or depleted, large uncleaved von Willebrand factor multimers aggregate in high shear areas of the microvasculature, leading to thrombotic microangiopathy. The main treatment for TTP is plasma exchange (PE) and corticosteroids. Refractory TTP, defined as

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progression of clinical symptoms during PE therapy, occurs in 10-20% of acquired TTP cases. For these patients, increased PE, and/or addition of cyclosporine or rituximab are current treatment options.

Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) are rare forms of vasculitis (inflammation of blood vessels) that affects the nose, lungs, kidneys, and other organs. Due to its end-organ damage, it is life-threatening and requires long-term immunosuppression. If the disease is limited, treatment with methotrexate plus glucocorticoids may be considered, but standard treatment for more severe disease is cyclophosphamide plus glucocorticoids. Rituximab may be used in combination with glucocorticoids for the treatment of patients with GPA or MPA.

Rheumatoid Arthritis (RA) is an autoimmune disease that causes inflammation of the joints and surrounding tissues, and most commonly occurs in patients between the age of 25 and 55 years old. It can lead to deformity through the stretching of tendons and ligaments and the destruction of joints. If it is not treated, RA can lead to loss of physical function and inability to carry out daily tasks of living. Disease modifying treatment includes anti-inflammatory agents such as NSAIDs as well as immunosuppressant agents such as methotrexate.

Autoimmune Hemolytic Anemia (AIHA) comprises direct Coombs-positive anemias including warm (80% of AIHA) and cold autoantibody types, and drug-induced AIHA. Warm AIHA is mediated by warm-reactive antibodies, primarily immunoglobulin G (IgG), that react optimally with human red blood cells in vitro at 37°C. Cold-reactive antibodies, primarily IgM, react maximally at 4°C. Cold AIHA, includes cold agglutinin syndrome and paroxysmal cold hemoglobinuria. Paroxysmal cold hemoglobinuria is generally self-limiting and has an excellent prognosis, so treatment with rituximab is not typically considered. Corticosteroids are first-line treatment in warm AIHA but less effective in cold AIHA.

Multicentric Castleman Disease (angiofollicular lymph node hyperplasia) is a rare lymphoproliferative disorder associated with human herpes virus-8 infection. Prevalence is increased among HIV-infected patients and associated with Kaposi sarcoma. Progression to lymphoma and mortality is high in these patients. Castleman disease has two distinct forms with characteristic findings on histologic examination: unicentric (hyaline vascular histology), and

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multicentric (plasma cell infiltrate). The clinical presentation typically involves lymphadenopathy and multiorgan involvement with an aggressive course. In HIV-non-infected patients, Multicentric Castleman disease typically presents after age 70 years. For HIV-infected patients, current guidelines suggest IV ganciclovir or oral valganciclovir for initial treatment based on level C evidence. Rituximab is considered an alternative therapy. Other treatments include combination chemotherapy and tocilizumab, a monoclonal anti-interleukin 6 antibody.

Neuromyelitis Optica (NMO) is a rare autoimmune inflammatory disorder that selectively affects the spinal cord and optic nerves; clinical presentation is characterized by severe optic neuritis that can lead to blindness and transverse myelitis that can lead to paralysis. The clinical course typically is more severe than multiple sclerosis, and often fatal. An autoantibody to aquaporin 4, a water channel found in high concentrations at the blood-brain barrier, is included in NMO diagnostic criteria. Curative treatment does not currently exist; treatment goals are: relapse remission, relapse prevention, and symptom relief. Immunosuppression with azathioprine or mycophenolate mofetil is commonly used for relapse prevention. Rituximab may also be considered for relapse prevention in NMO.

Lupus Nephritis (LN) is among the most serious complications of SLE. It occurs in approximately half of SLE patients and is associated with a poor prognosis. Estimated 5-year survival among patients with International Society of Nephrology/Renal Pathology Society class IV (diffuse) LN is 80%. At 10 years, 5-10% of LN patients will progress to end-stage renal disease. Current treatment regimens include cyclophosphamide or mycophenolate mofetil, both in combination with corticosteroids. Response rates at 1 year are 50-80%, but they are often only partial responses. The American College of Rheumatology 2012 guidelines state that in some cases, rituximab can be used in patients whose nephritis fails to improve or worsens after 6 months of one induction therapy, or after the patient has failed both cyclophosphamide and mycophenolate mofetil.

Chronic Graft versus Host Disease has been defined as graft versus host disease (GVHD) occurring more than 100 days after transplant. It is the primary cause of late morbidity and mortality after allogeneic hematopoietic cell transplantation. Approximately half of patients respond to first-line treatment of systemic corticosteroid with or without a calcineurin inhibitor (such as tacrolimus or cyclosporine), but those who do not respond have limited treatment options and poor prognosis. Rituximab has been studied in steroid-refractory chronic GVHD.

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Pemphigus and Pemphigoid Diseases occur when autoantibodies attack the epidermal cell junctions (pemphigus disease) or epidermal basement membrane (pemphigoid disease). Both classes of disease are characterized by blisters and erosions; however pemphigoid blisters are subepidermal and therefore tense, and pemphigus blisters are more superficial and therefore flaccid or often ruptured. Nikolsky sign—exfoliation and blister formation with skin friction—is negative in pemphigoid diseases and positive in pemphigus. Rituximab has been used successfully in combination with corticosteroids for initial management and treatment-refractory pemphigus as well as steroid-refractory pemphigoid diseases.

Idiopathic Membranous Nephropathy involves the abnormal thickening of the glomerular basement membrane and is a leading cause of nephrotic syndrome. Most membranous nephropathy cases are idiopathic, occurring from unknown causes, but secondary membranous nephropathy may result from other predisposing diseases, infection, or medical therapy. Secondary membranous nephropathy can be treated by removal of the offending drug or treatment of the underlying condition. In idiopathic membranous nephropathy, conservative treatment with renin-angiotensin system blockade is usually provided. Immunomodulatory agents (e.g. alkylating agents, calcineurin inhibitors, corticosteroids) are used to treat individuals who are unresponsive to conservative therapy. Rituximab may be used in patients with idiopathic membranous nephropathy who have failed previous treatment with other immunosuppressive regimens.

Autoimmune Encephalitis is a term that refers to syndromes that are associated with antibodies to neuronal cell surface/synaptic proteins. These syndromes have a wide clinical spectrum that ranges from typical limbic encephalitis to syndromes with complex neuropsychiatric symptoms such as deficits of memory, cognition, psychosis, seizures, abnormal movements, or coma. For some autoimmune encephalitides, children and women are more often affected. These disorders are highly responsive to immunomodulatory therapies including intravenous methylprednisolone, rituximab, or cyclophosphamide. It is important to recognize autoimmune encephalitis and begin treatment early because early initiation of treatment has been shown to improve outcomes, speed recovery, and reduce the risk of relapses. There are no controlled studies of any form of immunotherapy in patients with autoimmune encephalitis.

Multiple Sclerosis is believed to have an immunologic mechanism that is characterized by demyelination in the brain and spinal cord. This is often expressed by symptoms such as visual and

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oculomotor abnormalities, weakness, urinary dysfunction, and mild cognitive impairment. Often patients will experience remissions and exacerbations. Treatment can include corticosteroids for acute exacerbations and immunomodulatory (disease modifying) drugs to prevent exacerbations.

MuSK positive Myasthenia Gravis is a rare form of myasthenia gravis in which the patient has antibodies to MuSK, a receptor tyrosine kinase that mediates agrin-dependent AChR clustering and neuromuscular junction formation during development. Patients with this variant share many of the clinical manifestations of generalized myasthenia but tend to respond poorly to the anticholinesterase agents typically used for treatment of myasthenia gravis. Clinical practice guidelines published by the Myasthenia Gravis Foundation of America in 2020 recommend rituximab as an early therapeutic option in patients with MuSK antibodies who have an unsatisfactory response to initial immunotherapy. Additionally, a small, prospective, blinded nonrandomized comparative study found significantly better clinical outcomes in patients with anti-MuSK myasthenia treated using rituximab compared with those who did not receive rituximab.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is a group of related neuropathies that all have chronicity, demyelination, inflammation, and immune mediation. In the classic form of the condition, motor involvement is greater than sensory and the course is slowly progressive. However, a relapsing-remitting course occurs in at least one-third of patients and is more common in the pediatric age group. CIDP generally responds to immunosuppressive or immunomodulatory treatment with glucocorticoids, IVIG, or plasma exchange. In cases refractory to these treatments, rituximab may be considered.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In 1997 the FDA approved Rituxan for the treatment of relapsed or refractory, low-grade or follicular, CD20 positive, B-cell NHL. In 2006, the FDA granted Rituxan a supplemental approval for the treatment of diffuse large B-cell NHL in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or other anthracycline-based chemotherapy regimens in previously untreated patients.

In 2006 Rituxan was approved to be marketed specifically for the treatment of refractory RA.

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In January 2011, the FDA approved a new expanded indication for Rituxan for previously untreated follicular CD20-positive, B-cell NHL in combination with first-line chemotherapy and, in patients achieving a complete (CR) or partial response (PR) to Rituxan in combination with chemotherapy, as single-agent maintenance therapy.

In 2011, the prescribing information for Rituxan (rituximab) was expanded to include a new indication for use in combination with corticosteroids for the treatment of adults with WG and MPA.

In 2017, a subcutaneous formulation of rituximab with hyaluronidase, human (Rituxan Hycela) was approved by the FDA for use after at least one full dose of IV rituximab for the treatment of follicular lymphoma, previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens, and chronic lymphocytic leukemia in combination with fludarabine and cyclophosphamide (FC).

In 2018, Rituxan gained approval for the treatment of adult patients with moderate to severe pemphigus vulgaris. In addition, the label was updated to include information on follow up treatment of adult patients with GPA and MPA who have achieved disease control with induction treatment. The label was further expanded in September 2019 to include pediatric patients ages 2 years and older with GPA and MPA.

Truxima is a Rituxan biosimilar that was approved for the treatment of adult patients with NHL November 2018 and for the treatment of CLL in May 2019. The product was launched in November 2019. In May 2020, it was approved for the additional indications of rheumatoid arthritis and GPA and MPA.

Ruxience is a second Rituxan biosimilar that was approved in July 2019 for the treatment of adult patients with NHL, CD20-positive CLL, and GPA and MPA. In November 2021, the label was further expanded to include rheumatoid arthritis in adult patients.

Riabni, the third Rituxan biosimilar, was approved in December 2020 for the treatment of adult patients with NHL, CD20-positive CLL, and GPA and MPA. In June 2022, the label was further expanded to include rheumatoid arthritis in adult patients.

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Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Rituximab binds to the antigen CD20 found on normal and malignant B lymphocytes. Administration of rituximab results in a rapid and sustained depletion of circulating and tissue-based B-Cells. Lymph node biopsies performed 14 days after therapy showed a decrease in the percentage of B-cells in 7 of 8 patients with NHL who had received single doses of rituximab.

Non-Hodgkin's Lymphoma

2002 TEC criteria assessment approved the use of rituximab for patients with low-grade B-cell NHL who had not responded to standard treatments. It is designed to target and destroy white blood cells involved in the disease, resulting in significant tumor shrinkage. Because rituximab targets specific cells rather than all fast-growing cells there are fewer side effects than most chemotherapy. Patients are at an increased risk of developing infections since rituximab destroys healthy immune cells.

In NHL studies, administration of rituximab resulted in a rapid and sustained depletion of circulating and tissue-based B cells. Lymph node biopsies performed 14 days after therapy showed a decrease in the percentage of B-cells in 7 of 8 patients with NHL who had received single doses of rituximab. Circulating B-cells were depleted within the first 3 doses with sustained depletion for up to 6 to 9 months post-treatment in 83% of patients. B-cell recovery began at approximately six months following completion of treatment. Median B-cell levels returned to normal by 12 months following completion of treatment.

Subcutaneous rituximab (Rituxan Hycela) was studied in randomized controlled trials in patients with Follicular Lymphoma (FL), Diffuse Large B-cell Lymphoma (DLBCL), and Chronic Lymphocytic Leukemia (CLL).

The SABRINA trial was a phase 3 open-label randomized controlled trial evaluating subcutaneous rituximab in the treatment of FL. The study included 127 adults with previously untreated

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histologically confirmed CD20-positive FL with an Eastern Cooperative Oncology Group Performance Status score of 0 or 1 and a life expectancy of at least 6 months. Patients were randomized to IV rituximab plus chemotherapy (n=64) or subcutaneous rituximab plus chemotherapy (n=63). Patients in the subcutaneous group received 1 cycle of IV rituximab prior to receiving subcutaneous rituximab. The study was divided into two stages with the first stage assessing the pharmacokinetic noninferiority of rituximab via the rituximab serum trough concentration at induction cycle 7. Subcutaneous rituximab was found to be noninferior to IV rituximab since the serum trough concentration exceeded the prespecified margin. The overall rate of adverse events and the rate of grade 3 or 4 adverse events were similar in the 2 groups. However, administration-related adverse events were higher in the subcutaneous rituximab group (50%) than in the IV rituximab group (32%). The second stage of the study evaluated overall response rate via confirmed or unconfirmed complete response and partial response at the end of induction. An additional 282 patients were enrolled in the second stage, leading to 410 total patients evaluated (205 in the IV rituximab and 205 in the subcutaneous rituximab arm). At the end of induction, 84.9% of patients in the IV rituximab group and 84.4% of patients in the subcutaneous rituximab group achieved a complete response or partial response at the end of induction. The authors did not report a prespecified noninferiority margin for efficacy, but a nearly identical response rate indicates similar efficacy.

The MabEASE study evaluated subcutaneous rituximab in patients with previously untreated CD20-positive DLBCL. It compared subcutaneous rituximab (n=369) with IV rituximab (n=203), both in combination with CHOP. The primary outcome, investigator-assessed complete response rate at the end of combination treatment, was 47% in the subcutaneous rituximab group and 42% in the IV rituximab group. The difference in response rates was not statistically significant (4.9%; 95% CI, -3.6% to 13.5%). The incidence of adverse events, grade 3 or 4 adverse events, and administration-related adverse events were similar in both groups.

Chronic Lymphocytic Leukemia (CLL)
Current chemotherapy options for CLL include alkylating agents such as chlorambucil or cyclophosphamide (which when used as single agents have shown complete response rates <10%) and purine analogues such as fludarabine (with single-agent complete response rates of 20%). The combination of an alkylating agent and fludarabine improves the complete response rate to 40%.

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A 2012 Cochrane review compared monoclonal anti-CD20 antibodies with no further treatment or with other anti-leukemic therapies for treatment of CLL, irrespective of disease status. Both previously treated and chemotherapy-naïve patients were included, and all trials included were randomized and open-label. Three RCTs (total N=1421 patients) assessed the efficacy of rituximab plus chemotherapy compared with chemotherapy alone, and a meta-analysis found a statistically significant overall survival and progression free survival advantage for patients who received rituximab. Although there were more grade 3 and 4 adverse events in the rituximab arm, treatment-related mortality did not differ statistically between groups. Two RCTs (n=177 patients) evaluated rituximab and alemtuzumab; neither study reported progression free survival or overall survival. There was no statistically significant difference between arms for complete response rate or treatment-related mortality; however, more serious adverse events occurred in the alemtuzumab arm.

The SAWYER stage 2 trial was an open-label noninferiority randomized controlled trial that evaluated subcutaneous rituximab in the treatment of CLL. A total of 176 patients with previously untreated CLL were randomized to IV rituximab (n=88) or subcutaneous rituximab (n=88) plus fludarabine and cyclophosphamide for up to 6 cycles. Patients in the subcutaneous rituximab group received 1 cycle of IV rituximab prior to receiving subcutaneous rituximab. The primary end point was the rituximab serum trough concentration at cycle 5. Tumor response was included as an exploratory secondary outcome. Subcutaneous rituximab was found to be noninferior to IV rituximab because the serum trough concentration exceeded the prespecified margin. Adverse events were reported in 96% of the subcutaneous rituximab group and 91% of the IV rituximab group with the most common adverse events being neutropenia and nausea. In the exploratory analysis of tumor response 3 months after treatment, 85% in the subcutaneous rituximab group and 81% of patients in the IV rituximab group had an overall response. However, the authors noted that the study was not powered to detect differences in efficacy between the groups.

Hairy Cell Leukemia

In patients with relapsed or refractory HCL, retreatment with purine analogs has been observed to result in shorter remission durations with each successive treatment. Thus, rituximab has been studied in combination with purine analogs in patients with relapsed or refractory HCL. In a phase II study that included 14 patients with relapsed HCL, cladribine followed by rituximab resulted in a complete response rate of 100%. After a median follow up of 60 months, the 5-year failure-free survival and overall survival rates were 100%. In a retrospective study of 18 patients with pretreated

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HCL relapsing after purine analog monotherapy (median 2 prior therapies), rituximab in combination with pentostatin or cladribine resulted in a complete response rate of 89%. Complete response was maintained in all patients after a median follow up of 36 months and the estimated 3-year recurrence rate was 7%.

Rituximab monotherapy has modest activity in HCL that has relapsed after initial treatment with a purine analog. In a small cohort of 10 patients with HCL progressing on prior therapy with cladribine or pentostatin, rituximab monotherapy resulted in an overall response rate of 50% with complete response in only 10% of patients. In another study of 24 patients with relapsed HCL after prior therapy with cladribine, rituximab induced an overall response rate of only 25% with a complete response in 13%. In a smaller study of 15 patients with relapsed or primary refractory HCL after treatment with purine analogs, 8 weekly doses of rituximab (Rather than the standard 4 weekly doses) resulted in overall response rates and complete response rates of 80% and 53%, respectively. In another phase II study of 25 patients with less heavily pretreated HCL relapsing after cladribine, the overall response rate and complete response rates with rituximab were 80% and 32%, respectively.

Waldenstrom Macroglobulinemia
Rituximab in Waldenstrom macroglobulinemia was studied in a two prospective phase II studies in patients with symptomatic disease. The first study included 34 untreated and 35 previously treated patients who were all administered rituximab 375 mg/m^2 weekly for 4 consecutive weeks. Of the 69 patients evaluable for response, 19 (27.5%) achieved an objective response and 17 (24.6%) achieved a minor response. The overall response rate was 52.2% (90% CI[41.6%, 62.6%]). Of previously untreated patients, 35.3% vs. 20% of previously treated patients achieved an objective response. Median response duration was not significantly different between previously untreated and previously treated patients. The second study included 27 patients treated with rituximab 375 mg/m^2 IV weekly for 4 weeks. Three months after completion of regimen, patients without evidence of progressive disease received repeat 4-week courses of this agent. 44% of the 27 patients achieved a partial response after treatment with rituximab. Median time to response was 3.3 months (range 2.2 to 7.1 months). Responses occurred in 40% of the 15 previously untreated patients and 50% of the 12 pretreated patients. The median time to progression for all patients was 16 months, and with a median follow-up of 15.7 months. Treatment with rituximab was well tolerated, with approximately 25% of patients experiencing some mild form of infusion-related toxicity, usually fever and chills.

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Thrombocytopenic Purpura
Two systematic reviews in ITP of primarily observational studies and 2 randomized controlled trials in adults investigated mostly non-splenectomized patients. Overall and complete response rates were approximately 57% and 40%, respectively, in adults, and 68% and 39% in children. Median response durations were approximately 1 year. Adverse event reporting was inconsistent; serious infections and hypersensitivity reactions occurred in 4% of 370 children included in the systematic review. A placebo-controlled randomized trial evaluating rituximab as second-line therapy did not demonstrate benefit compared with placebo.

Rituximab for the treatment of TTP was studied in a single phase 2 cohort study and several case series. The phase 2 cohort study included 40 patients with anti-ADAMTS13 antibody-positive, new-onset or acute relapsed TTP compared to an age-, sex-, and ethnicity-matched historical control group of 40 patients. Enrolled patients received rituximab 375 mg/m^2 weekly for 4 weeks. All patients and historical controls received plasma exchange at admission and then daily until remission. The primary efficacy outcome was the number of plasma exchange treatments to remission. The rituximab-treated patients received a median of 16.5 treatments compared with 18 treatments in the historical control group (p=0.5). Among secondary outcomes, there was no statistical difference between groups in the number of hospital admission days, but among patients who relapsed (4 in the rituximab group, 21 in the control group), median time to relapse was longer in the rituximab-treated patients (27 months) than in historical controls (18 months). Both incidence of infections and serious adverse events were similar between groups.

Tun et al (2012) conducted a systematic review of 15 case series and 16 case reports (total N=100 patients) of immune-mediated, relapsed or refractory TTP treated with rituximab. 98% of patients achieved complete response. During median follow-up of 13 months, 9% of patients who achieved complete response relapsed. Anti-ADAMTS13 antibody positivity and severe ADAMTS13 deficiency predicted response to rituximab. Serious rituximab-related adverse events occurred in 3% of patients.

Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)
FDA approval for rituximab as initial treatment in GPA and MPA was based on 1 active-controlled randomized trial, the Rituximab in ANCA-Associated Vasculitis (RAVE) noninferiority trial.

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Patients 15 years of age or older who had severe GPA or MPA were enrolled. Patients with Churg-Strauss syndrome, severe alveolar hemorrhage, or severe kidney disease were excluded. Patients were randomized to rituximab 375 mg/m^2 weekly for 4 weeks followed by oral placebo beginning at 3 to 6 months or cyclophosphamide 2 mg/kg orally daily for 3 to 6 months followed by oral azathioprine daily beginning at 3 to 6 months. All patients received 1 to 3 pulse doses of parenteral methylprednisolone 1000 mg followed by prednisone 1 mg/kg orally daily. Patients who achieved remission tapered and discontinued prednisone by month 5. At 6 months, 63% of patients in the rituximab group and 52% of patients in the cyclophosphamide group achieved complete remission, for a treatment difference of 11 percentage points which exceeded the prespecified noninferiority margin of -20 percentage points. The incidence of adverse events was similar between treatment groups, with grade 2 or higher leukopenia more common in the cyclophosphamide group (10% vs 3% rituximab) and hospitalizations due to disease or treatment more common in the rituximab group (8% vs 2% cyclophosphamide).

FDA recommendations for follow up treatment of GPA and MPA was based on 1 open-label, prospective, randomized, active-controlled study including 115 patients. Eligible patients were 21 years and older and had either newly diagnosed (80%) or relapsing disease (20%). Remission of active disease was achieved using a combination of glucocorticoids and cyclophosphamide. Within a maximum of 1 month after the last cyclophosphamide dose, eligible patients were randomized in a 1:1 ratio to receive either rituximab or azathioprine. The primary endpoint was the occurrence of major relapse (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) through month 28.By month 28, major relapse occurred in 3 patients (5%) in the rituximab group and 17 patients (29%) in the azathioprine group. The observed cumulative incidence rate of first major relapse during the 28 months was lower in patients on rituximab relative to azathioprine.

FDA recommendations for the treatment of pediatric patients with GPA or MPA were based on a multicenter, open-label, single-arm, uncontrolled study in 25 pediatric patients aged 6-17 years of age with active GPA or MPA. The study design consisted of an initial 6-month remission induction phase with rituximab, and a minimum 12-month follow-up phase up to a maximum of 54 months. Patients were to receive a minimum of 3 doses of IV methylprednisolone prior to the first rituximab infusion. If clinically indicated, up to 3 additional daily doses of IV methylprednisolone could be given. The remission induction regimen consisted of four once weekly intravenous infusions of

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rituximab at a dose of 375 mg/m^2 BSA, on study days 1, 8, 15, and 22 in combination with oral prednisolone or prednisone at 1 mg/kg/day tapered to 0.2 mg/kg/day minimum by month 6. After the remission induction phase, patients could receive subsequent rituximab on or after month 6 to maintain remission and control disease activity. The primary objectives of this study were to evaluate safety and pharmacokinetic parameters in pediatric GPA and MPA patients. The efficacy objectives were exploratory and principally assessed using the Pediatric Vasculitis Activity Score (PVAS). PVAS remission was defined by a PVAS of 0 and achievement of glucocorticoid taper to 0.2 mg/kg/day or a PVAS of 0 on two consecutive readings ≥4 weeks apart irrespective of glucocorticoid dose. All 25 patients completed all four once weekly infusions for the 6-month remission induction phase and 24/25 completed at least 18 months from day 1. At month 6, the PVAS remission rate was 56%, at month 12 it was 92%, and at month 18 it was 100%.

Rheumatoid Arthritis (RA)
B-cells are believed to play a role in the pathogenesis of RA and associated chronic synovitis. In this setting, B-cells may be acting at multiple sites in the autoimmune/inflammatory process, including through production of rheumatoid factor (RF) and other auto antibodies, antigen presentation, T-cell activation and/or pro-inflammatory cytokine production.

FDA approval of rituximab for RA was based on 4 placebo-controlled, randomized trials. Three trials enrolled adults with moderately to severely active RA who had a previous inadequate response to at least 1 TNF inhibitor. In the REFLEX trial, patients who received a single course of rituximab with concomitant methotrexate had statistically significant and clinically meaningful improvements in disease activity at 24 weeks (as assessed by 20%, 50%, and 70% improvements in American College of Rheumatology [ACR] response criteria) compared with patients who received placebo. At 48 weeks, progression of joint space narrowing and erosion at 48 was less in patients who received rituximab: 60% of patients in the rituximab group had no progression of structural damage compared with 46% in the placebo group. In the SUNRISE trial, patients who received 2 courses of rituximab approximately 6 months apart had improved ACR20 scores at 48 weeks compared with those who received only 1 course of rituximab. A third trial showed statistically significant and clinically meaningful improvements in physical function at 24 and 48 weeks in patients who received an initial course of rituximab 500 mg or 1000 mg compared with patients who received placebo. The IMAGE randomized controlled trial compared rituximab 500 gm with 1000 mg dosing in methotrexate-naïve patients. All patients received methotrexate. Patients who had active disease at

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24 weeks could receive another course of rituximab at their assigned dose. At 48 weeks, the proportion of patients achieving clinically meaningful responses was similar in both rituximab groups and greater than placebo. However, compared with placebo, a statistically significant (67%) reduction in joint space narrowing and erosion was observed in the rituximab 1000 mg group only.

Autoimmune Hemolytic Anemia (AIHA)
Rituximab for treatment-refractory idiopathic warm AIHA has been studied in 3 case series described in a 2011 systematic review (total N=42 patients). The overall response rate was 93% with 43% experiencing complete response and 50% experiencing partial response. Based on these results, reviewers recommended rituximab 375 mg/m^2 weekly for 4 weeks or splenectomy for relapsed or refractory warm AIHA.

In patients with newly diagnosed warm AIHA, 2 randomized controlled trials have demonstrated efficacy of rituximab compared to prednisolone alone or placebo. In the first trial, 64 patients newly diagnosed with idiopathic or secondary warm AIHA were randomized to rituximab plus short course prednisolone or prednisolone alone. At 12 months, the overall response rate was 75% in the rituximab group and 36% in the control group (p=0.003). Serious adverse events occurred in 28% of the rituximab-treated patients and 17% of the control patients. The second trial compared patients with recently-diagnosed warm AIHA given rituximab (N=16) to those given placebo (N=16). All patients were treated with methylprednisolone prior to receiving 2 infusions of rituximab or placebo, 2 weeks apart. After 1 year, overall response rates were 75% in the rituximab group and 31% in the placebo group (p-0.032). Serious adverse events occurred in 4 patients in the rituximab group and 7 patients in the placebo group.

In a 2008 review of cold AIHA, Petz identified 11 case reports and case series of rituximab in cold agglutinin syndrome. In 2 case series (total N=47 patients), the overall response rate was 62%. The median duration of response in 20 responders was 11 months, and no serious adverse events were reported in 20 rituximab-treated patients. Based on this evidence, Petz suggested rituximab as a treatment option for cold agglutinin syndrome, along with avoidance of cold and immunosuppressive drugs.

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Multicentric Castleman Disease
Almost all of the evidence for rituximab in Multicentric Castleman Disease is based on studies in HIV-infected patients. A 2012 literature review identified 1 prospective and 2 retrospective cohort studies (total N=69 patients). In the prospective study, estimated 2-year overall survival was 95%. One retrospective study compared the incidence of subsequent NHL in 33 rituximab-treated patients with the incidence in non-rituximab-treated patients. All rituximab-treated patients had received first-line chemotherapy. Three-year NHL incidence was 0.04% in the rituximab group compared with 23% in non-rituximab-treated patients. Median overall survival rates were 15.7 years and 5.2 years in the rituximab and control groups, respectively.

Gerard et al (2012) reported on a prospective cohort of 113 HIV-infected patients who had Multicentric Castleman disease. The authors compared the incidence of subsequent NHL in rituximab-treated (n=48) with that in non-rituximab-treated (n=65) patients. At a mean follow-up of 4.2 years, annual NHL incidence was 0.004% in the rituximab group and 7% in the control group. (HR=0.09). Two and 5 year overall survival rates were 93% and 90%, respectively, in the rituximab group, and 68% and 47% in the control group. Ten Kaposi sarcoma exacerbations and 1 newly diagnosed Kaposi sarcoma were observed in 9 patients after rituximab therapy. Amon the 36 rituximab responders, multicentric Castleman disease recurred in 8 (22%) after a median of 10.5 months.

Neuromyelitis Optica
The evidence base for use of rituximab to prevent relapse in NMO is comprised of uncontrolled observational studies and systematic review. A 2016 systematic review of 46 uncontrolled studies (total N=438 patients) evaluated the annualized relapse rates ratio and the EDSS score before and after treatment. A meta-analysis of the 25 studies providing data on the annualized relapse rates ratio found significant reduction after therapy. The pooled mean reduction after rituximab therapy was 0.79. Eighteen studies were included in a meta-analysis of EDSS scores. There was a significant reduction in the EDSS score after treatment (mean reduction, 0.64; 95% CI, -1.18 to -0.10). Overall, adverse events were reported in 113 (26%) of 438 patients. The most common adverse events were infusion-related events and infections. Seven patients died; it was not reported whether the deaths were likely to be treatment-related.

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In a retrospective review of 90 patients with NMO previously treated with multiple sclerosis treatments (e.g. β-interferon, glatiramer acetate), the efficacy of rituximab appeared comparable with that of azathioprine and mycophenolate mofetil. Reductions in annualized relapse rates were found to be 88% with rituximab, 87% with mycophenolate mofetil, and 72% with azathioprine.

A retrospect-prospective cohort has suggested rituximab as, or possibly more, effective than other agents in preventing relapse. 71 patients with NMO or related NMO spectrum disorder were retrospectively identified and followed-up with by telephone to ascertain disease status. Rituximab (n=32), azathioprine (n=22), mycophenolate (n=11), and cyclophosphamide (n=5) were given to 54 patients. Reported decreases in annualized relapse rates were: rituximab, 0.92, azathioprine, 0.36; mycophenolate, 0.67; and cyclophosphamide, 0.38. corresponding adverse event rates by agents were: rituximab, 25%; azathioprine, 36%; mycophenolate, 36%; and cyclophosphamide, 80%.

Lupus Nephritis (LN)
Evidence for the use of rituximab in LN includes a systematic review, a randomized controlled trial, a registry study, and several case series and case reports. The systematic review of rituximab in refractory LN included 9 prospective comparative studies, 9 retrospective studies, and 8 case series and case reports (total N=300 patients). 39% of patients had class IV nephritis, but 30% were unclassified. Rituximab dosing and use as alternative or add-on therapy varied across studies; the most common dosing regimen was 375 mg/m^2 weekly for 4 weeks. Mean follow-up was 60 weeks (range, 12-120 weeks). Rituximab induced a complete, partial, or no response in 40%, 34%, and 26% of cases, respectively. Complete responses and any responses were most frequent in patients with class III (focal) LN and least frequent in patients with class V (membranous) LN.

One of the RCTs identified in the systematic review previously described was the 2012 double-blind LUNAR (Lupus Nephritis Assessment with Rituximab) trial. LUNAR was a randomized, double-blind, placebo-controlled phase 3 trial of rituximab plus mycophenolate and corticosteroids as initial therapy for proliferative LN. The trial included 144 patients 16 to 75 years of age who had histologic evidence of class III or IV LN on biopsy within 12 months before randomization. Patients were randomized to IV rituximab 1000 mg at weeks 1, 3, 24, and 26 or placebo in combination with mycophenolate and prednisone. The primary efficacy end point, superior overall (complete or partial response) renal response rate at 1 year with rituximab, was not reached (57% [26% complete response, 31% partial response] in the rituximab group vs 46% [31% complete response, 15% partial

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response] in the placebo group; p=0.18). Incidence of serious adverse events did not differ statistically between groups. An accompanying editorial observed that the trial was powered to detect a 20% increase in complete renal response and a 5% increase in partial renal response; it was underpowered to detect a difference comprising mainly partial responses.

In 2012, Diaz-Lagares et al reported on pooled results from the UK-BIOGEAS Registry and published European studies. The UK-BIOGEAS Registry was jointly developed in the U.K. and Spain to evaluate the use of rituximab in LN. Among a total of 164 patients (99 registry patients, 65 patients in published studies), most (57%) had class IV LN. Rituximab was administered in combination with corticosteroids in 99% of patients and with immunosuppressive agents (cyclophosphamide or mycophenolate) in 76% of patients. Half of patients were refractory to standard treatment, 42% were treated for disease flare, and 8% were treated at first presentation of LN. At 6 and 12 months, respectively, renal response rates (using standard definitions) were 27% and 30% for complete response, 40% and 37% for partial response, and 33% at both time points for no response. Overall (complete or partial) responses were more common in patients with class III LN than in patients with class IV or V LN (p=0.007 and 0.03 respectively). Two patients developed severe infusion reactions. Twenty (12%) patients had 21 infections, most commonly respiratory infections. Six (4%) patients developed neutropenia after rituximab administration. Three (2%) patients developed posterior reversible leukoencephalopathy.

Chronic Graft versus Host Disease (GVHD)
Rituximab for treatment of steroid-refractory chronic GVHD has been examined in cohort studies, which have shown responses in most patients, with sustained responses and steroid reductions or discontinuations in some.

In 2009, Kharfan-Dabaja published a systematic review and meta-analysis of 7 cohort studies (total N=111 patients) of rituximab in chronic GVHD. Three studies were prospective, and four were retrospective. Pooled overall response rate was 66% (95% CI, 57-74%). Indication-specific response rates were 13-100% for skin, 0-83% for oral mucosa, 0-66% for liver, and 0-38% for lung. Common adverse events were infusion reactions or infectious complications.

In 2010, Kim et al published a multicenter, phase 2 cohort study of 37 patients with steroid-refractory chronic GVHD diagnosed according to National Institute of Health criteria. Most transplants used

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myeloablative conditioning regimens (78%) ad unrelated donor cells. Patients received rituximab 375 mg/m^2 weekly for 4 weeks and then monthly for 4 months; 29 patients completed treatment, and 22 completed 8 additional months of follow-up. 32 (86%) patients had any response (complete or partial) at any time during the study; median time to response was 29 days (range 0-252 days). 21 (57%) patients maintained response for 1year, of whom 6 discontinued and 15 reduced steroid therapy. Response rates were higher for skin, oral mucosa, and musculoskeletal symptoms (response rates 71-100%) than for other organs (e.g., 9% for lung involvement). Most treatment failures were due to infectious complications or relapse of the primary disease.

Pemphigus and Pemphigoid Diseases
In patients with newly diagnosed pemphigus, there is one randomized controlled trial and a few small case series demonstrating efficacy with rituximab treatment. Case series had sample sizes ranging from 5 to 10 patients with untreated pemphigus. The series generally found rituximab, along with corticosteroids to be beneficial in terms of response and remission rates; however the studies lack a comparison group with first-line corticosteroids alone. The randomized controlled trial was unblended and compared first-line treatment with corticosteroids plus rituximab to corticosteroids alone in 91 adult patients with newly diagnosed pemphigus. Patients were randomized to corticosteroid treatment alone (i.e., an initial high dose of prednisone tapered over 12 to 18 months) or short-term corticosteroid treatment plus rituximab (i.e., an initial high dose of prednisone with rapid tapering over 3 to 6 months plus IV rituximab, 100 mg on days 1 and 14, and 500 mg at months 12 and 18). The primary end point was the proportion of patients who achieved complete response at month 24, defined as the absence of new or established lesions with the patients off corticosteroids for at least 2 months. At 24 months, 89% of the 46 patients in the rituximab plus corticosteroid group and 34% of the 44 patients in the corticosteroid-only group achieved a complete response. The difference between groups was statistically significant ($p<0.001$). This degree of difference corresponded to a number needed to treat with initial combined treatment of 1.82. Patients in the rituximab plus corticosteroid group took a significantly lower cumulative dose of corticosteroids during the study than the corticosteroid-only group (6143 mg vs 17,974 mg).

In pemphigus refractory to first-line treatment, evidence for rituximab includes a case series of 42 patients with refractory pemphigus vulgaris with severe mucous or mucocutaneous involvement or pemphigus foliaceus and two retrospective cohort studies. In the case series, patients received rituximab 1000 mg/m^2 every 2 weeks for 2 doses plus corticosteroids only; IVIG or

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immunosuppressive drugs were not given. At the median follow up of 26.5 months, 36% of 42 patients achieved a complete response and discontinued steroids within 6 months. 14% of patients had a partial response and achieved complete response after an additional infusion of IV rituximab 500 mg. 48% of patients relapsed, each of whom received an additional infusion of IV rituximab 500 mg and achieved a complete response. No serious adverse events were observed. Similar results were seen in the retrospective cohort studies with one study of a fixed-dose rituximab in refractory pemphigus vulgaris and pemphigus foliaceus observing complete remission in 89% of 84 patients and the other finding 100% of 49 patients achieving disease control with rituximab compared to only 40% of patients receiving conventional immunosuppression.

Only 3 of 8 pemphigoid diseases were examined in the literature: epidermolysis bullosa acquisita, bullous pemphigoid, and mucous membrane pemphigoid. A 2013 review of treatment options for pemphigoid diseases found evidence for rituximab in refractory bullous pemphigoid in combination with first-line treatments, such as topical or oral corticosteroid and some immunosuppressive drugs; refractory mucous membrane pemphigoid in combination with immunosuppressive drugs, such as dapsone and/or sulfasalazine; and refractory epidermolysis bullosa acquisita in combination with systemic corticosteroids.

A 2013 systematic review of rituximab for treatment of refractory bullous pemphigoid identified 1 case series and 8 case reports (total N=16 patients), including 4 children. 14 patients received IV rituximab 375 mg/m^2 weekly for 4 doses, and 2 received 1000 mg every other week for 2 doses. All patients received concomitant immunosuppressive therapy and/or IVIG. Mean follow-up was 15.6 months (range, 1-36 months). 69% of the 16 patients had a complete response, 6% had a partial response, 6% had no response, and 19% died.

A systematic review of rituximab for the treatment of refractory mucous membrane pemphigoid was also conducted in 2013 including studies that dosed rituximab at 375 mg/m^2 weekly for 4 weeks. 1 case series and 6 case reports were identified (total N=28). Median follow-up ranged from 9 to 31 months. All patients received concomitant immunosuppressive and/or immunoadsorbent therapy. 71% of 28 patients had a complete response, 11% had a partial response, 7% were nonresponders, and 4% had progression of disease leading to blindness and was considered a treatment failure. One patient died from infection. Approximately half of patients received a second rituximab cycle because of relapse or lack of response.

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Foster et al (2010) reported a retrospective comparative study of 12 patients who had refractory mucous membrane pemphigoid of the eye (ocular cicatricial pemphigoid), 10 of whom were blind in 1 eye. Six patients received rituximab 375 mg/m^2 weekly for 8 weeks plus IVIG, and 6 patients received immunosuppressive therapy (cyclophosphamide or infliximab) plus IVIG. At the median follow-up of 11 months, visual acuity was preserved, and no progression of disease observed in the rituximab group. By contrast, all 6 control patients progressed to blindness in both eyes. No adverse events were observed in the rituximab group.

Idiopathic Membranous Nephropathy
Evidence for rituximab in the treatment of idiopathic membranous nephropathy includes multiple observational studies and a randomized controlled trial. This evidence demonstrates that rituximab may have moderate benefit in patients with idiopathic membranous nephropathy who have failed previous treatment with other immunosuppressive regimens or those with a moderate risk of progression who have not previously received immunosuppressive therapy. However, a longer randomized controlled trial is needed to confirm the benefits of rituximab and to determine the optimal schedule, dose, and long-term safety and efficacy.

The randomized controlled trial was unblinded and included 75 patients with persistent proteinuria (>3.5 g/d). Patients were randomized to rituximab or no rituximab groups. At 6 months, there was no significant difference in the primary composite end point of complete (<500 mg/d) or partial (<3.5 g/d with ≥50% reduction vs baseline) remission of proteinuria between patients treated with (35%) or without rituximab (21%). The lack of benefit was attributed in part to the short duration of the trial. In a post trial observational phase that followed patients for an additional 12 months, the rate of complete or partial remission was higher among patients treated with rituximab (65% vs 34%). In addition, patients treated with rituximab had lower proteinuria and higher serum albumin levels. These findings are consistent with observational studies that have demonstrated a maximal reduction in proteinuria at 18 to 24 months after treatment with rituximab.

A 2016 multicentric prospective study evaluated 34 patients with membranous nephropathy who received rituximab once (n=18) or twice (n=16). Rituximab was the first-line therapy for 19 (56%) and second-line for 15 (44%) patients. At 12 months, 5 (14.7%) patients achieved complete response, 10 (29.4%) partial, and 19 (55.8%) no response. Response occurred approximately 6 months later. At 24 months, the clinical situation was unchanged: 2 nonresponders achieved partial response and

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2 responders relapsed. Authors concluded that low-dose rituximab resulted in remission in less than 50% of patients with idiopathic membranous nephropathy. It is possible that higher doses and longer treatments are needed to induce and maintain a response.

Hepatitis C Virus–Associated Cryoglobulinemic Vasculitis
Recent reviews have summarized the literature on rituximab for the treatment of HCV-associated cryoglobulinemic vasculitis. Across 2 randomized controlled trials and many observational studies (total N=377 patients), the median overall response was approximately 80%. However, these studies were done before the advent of direct-acting antiviral treatment and pegylated interferon–free drug regimens for HCV infection. More effective antiviral treatments should improve outcomes (eg, virologic and immunologic responses, cure rate) of both HCV and associated vasculitis. However, for patients with antiviral-resistant active disease or with severe or life-threatening cryoglobulinemic vasculitis, rituximab in combination with current treatments may improve health outcomes. Viral load and liver function tests should be monitored during rituximab treatment. A phase 2 trial has suggested low-dose rituximab may have similar efficacy as high-dose treatment with and fewer adverse events.

Multiple Sclerosis
Two randomized controlled trials have evaluated rituximab in patients with multiple sclerosis. One trial in patients with relapsing remitting multiple sclerosis showed improvements using MRI and in clinical outcomes at 24-week follow-up. However, methodologic limitations restrict the conclusions that can be based on these data. The second trial, which was well-designed and was conducted in patients with primary progressive multiple sclerosis, demonstrated no effect of rituximab on disease progression. A large registry study found a relatively low rate of adverse events and relapses and little change in disability scores; this study lacked a comparison group.

In 2017, the FDA approved ocrelizumab (Ocrevus™)‡ for the treatment of multiple sclerosis. Ocrevus is a CD20 directed cytolytic antibody with a similar mechanism of action to rituximab and demonstrated efficacy in multiple sclerosis. Thus, it is the preferred agent of treatment for patients with multiple sclerosis who may otherwise be candidates for rituximab. The patient selection criteria presented in this policy take into consideration patient history of a clinical response and stabilized regimen of rituximab for multiple sclerosis. In the absence of the above mentioned caveat, there is no advantage of using rituximab over Ocrevus or another available multiple sclerosis treatment.

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MuSK Positive Myasthenia Gravis

Hehir et al (2017) conducted a prospective blinded nonrandomized comparative study in patients with anti-MuSK myasthenia gravis. Twenty-four patients were treated with rituximab and 31 received standard care without rituximab treatment. The primary outcome was the Myasthenia Gravis Status and Treatment Intensity (MGSTI) score. MGSTI scores range from level 0 (complete stable remission; no immunotherapy) to level 6 (symptomatic and requiring hospitalization). The authors defined as beneficial clinical outcome as an MGSTI score of level 2 or better. Level 2 was defined as having minimal manifestations/pharmacologic remissions with a low dose of dual therapy. A secondary outcome was an MGSTI score of level 1 or better (minimal manifestations/pharmacologic remissions with a low dose of oral monotherapy). Fifty-eight percent of patients in the rituximab arm had a successful clinical outcome (i.e., MGSTI score of level 2 or better) compared with 16% of controls; the difference between groups was statistically significant (p=0.002). The median time to achieve an MGSTI score of level 2 or better for patients in the rituximab arm was 54 months. In addition, 54% of patients in the rituximab arm achieved the more stringent outcome of MGSTI score of level 1 or better at the final evaluation compared with 26% in the control arm (p=0.003).

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Policy History

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10/04/2006	Medical Director Review
10/18/2006	Medical Policy Committee approval
12/05/2007	Medical Director review
12/19/2007	Medical Policy Committee approval. Coverage eligibility changed for treatment of Waldenstrom's Macroglobulinemia and Idiopathic Thrombocytopenia Purpura.
12/03/2008	Medical Director review
12/17/2008	Medical Policy Committee approval. No change to coverage eligibility.
12/04/2009	Medical Policy Committee approval

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12/16/2009	Medical Policy Implementation Committee approval. Added that when patient selection criteria are not met, or if infliximab is used for non-FDA approved indications, to deny investigational.
12/01/2010	Medical Policy Committee review
12/15/2010	Medical Policy Implementation Committee approval. Format revision; including, addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
06/02/2011	Medical Policy Committee review
06/15/2011	Medical Policy Implementation Committee approval. Added coverage for use in combination with corticosteroids for the treatment of adults with Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)
06/14/2012	Medical Policy Committee review
06/20/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/06/2013	Medical Policy Committee review
06/25/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/05/2014	Medical Policy Committee review
06/18/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/04/2015	Medical Policy Committee review
06/20/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
06/02/2016	Medical Policy Committee review
06/20/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-10 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. Added 9 off-label indications based on the BCA policy (thrombotic thrombocytopenic purpura, warm autoimmune hemolytic anemia, cold agglutinin syndrome, multicentric Castleman

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	disease, Neuromyelitis Optica, Lupus Nephritis, chronic graft-versus-host disease, pemphigus, and pemphigoid disease) as well as a new drug formulation (Rituxan Hycela).
12/06/2018	Medical Policy Committee review
12/19/2018	Medical Policy Implementation Committee approval. Updated patient selection criteria to include coverage for relapsed hairy cell leukemia, autoimmune encephalitis, cryoglobulinemic vasculitis, and patients with MS previously stabilized on rituximab. Updated background information to reflect new FDA approvals for pemphigus vulgaris and follow up treatment in GPA/MPA.
06/17/2019	Coding update
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. Updated age approval and relevant background information for GPA/MPA. Added new biosimilar, Truxima.
09/03/2020	Medical Policy Committee review
09/09/2020	Medical Policy Implementation Committee approval. Added coverage for CD20+ ALL to reflect update in NCCN guidelines. Added new biosimilar, Ruxience. Updated criteria for thrombocytopenia to allow for coverage of ITP in patients who have failed glucocorticoids.
04/01/2021	Medical Policy Committee review
04/14/2021	Medical Policy Implementation Committee approval. Added new biosimilar, Riabni. Updated title
04/07/2022	Medical Policy Committee review
04/13/2022	Medical Policy Implementation Committee approval. Added criteria to allow coverage of MuSK positive myasthenia gravis. Noted expanded indication for Ruxience in background.
04/06/2023	Medical Policy Committee review
04/12/2023	Medical Policy Implementation Committee approval. Added criteria to allow coverage of CIDP. Updated background information to reflect new approval of Riabni for RA.
04/04/2024	Medical Policy Committee review
04/10/2024	Medical Policy Implementation Committee approval. Added new criterion to require trial and failure of Rituxan and Ruxience prior to use of Truxima or Riabni.

Next Scheduled Review Date: 04/2025

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J9311, J9312, Q5115, Q5119, Q5123
ICD-10 Diagnosis	All related diagnoses

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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

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