Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Rituximab Agents (Including Rituxan Hycela®) for Non-Oncology and Oncology-Related Indications	MP-RX-FP-78-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of Rituximab agents (Rituxan®, Truxima® [rituximab-abbs], Riabni® [rituximab-arrx], and Ruxience® [rituximab-pvvr]), a genetically engineered monoclonal antibody that targets CD20 found on the surface of normal and malignant B-lymphocytes, approved by the Food and Drug Administration (FDA), and used off-label, for the treatment of various oncology and non-oncology conditions. This document also addresses the use of Rituxan Hycela® (rituximab and hyaluronidase), a rituximab-formulation that contains hyaluronidase, indicated to be administered subcutaneously for patients with certain oncology-related conditions who have already used at least one dose of rituximab i.v.

Background Information

Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD located on pre-B and mature B lymphocytes. The antigen is expressed on > 90% of B-cell Non-Hodgkin's Lymphomas (NHL), but the antigen is not found on hematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissues.

Initially used for anti-neoplastic therapy, it has been licensed for use in several autoimmune disorders. Labeled uses for Rituximab include chronic lymphocytic leukemia, non-Hodgkin lymphomas, pemphigus vulgaris, rheumatoid arthritis, Antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis (which includes microscopic polyangiitis, granulomatosis with polyangiitis (GPA) (formerly Wegener's Granulomatosis) and eosinophilic GPA (formally Churg–Strauss syndrome). It is thought to act primarily by depleting CD20-positive cells. Rituximab has been used off-label for a multitude of indications. Rituximab carries a black-box warning about the following risks associated with rituximab use: fatal infusion reactions, tumor lysis syndrome, severe skin and mouth reactions, hepatitis B virus reactivation, and progressive multifocal leukoencephalopathy.

The FDA initially approved Rituximab on November 26, 1997. An alert was issued on September 25, 2013, by the FDA to highlight additional Boxed Warning information about Rituximab regarding patients with prior Hepatitis B virus (HBV) infection; HBV reactivation may occur when the body's immune system is impaired. HBV cases and patient deaths continued to occur. In response, the FDA recommends screening and monitoring prior to and throughout rituximab's duration in patients with prior HBV infection.

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Rituxan Hycela® is a combination of rituximab and hyaluronidase human, an enzyme that facilitates the delivery of rituximab under the skin, indicated for the treatment of adult patients with various lymphoma conditions, including follicular lymphoma (FL), relapsed or refractory follicular lymphoma, previously untreated follicular lymphoma in combination with first-line chemotherapy, non-progressing follicular lymphoma after first-line CVP chemotherapy, previously untreated diffuse large B-cell lymphoma (DLBCL), and previously untreated and previously treated chronic lymphocytic leukemia (CLL) in combination with FC.

Treatment with Rituxan Hycela should be initiated only after patients have received at least one full dose of a rituximab product by intravenous infusion, and it is not intended for the treatment of non-malignant conditions. Rituxan Hycela provides an alternative route of administration compared to intravenous Rituxan, as it is given subcutaneously, but it should not be administered before intravenous Rituxan to avoid adverse effects.

Rituxan Hycela® is unproven and not medically necessary for the treatment of non-oncology indications.

- **Non-Oncology Related Indications**

Rituximab is FDA approved for the non-oncologic uses of rheumatoid arthritis, pemphigus vulgaris, and granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).
Rheumatoid Arthritis: The American College of Rheumatology (ACR) guidelines recommend disease-modifying antirheumatic drug (DMARD) monotherapy as first-line treatment in individuals with RA with moderate to high disease activity. Methotrexate (MTX) monotherapy, titrated to a dose of at least 15 mg, is recommended over hydroxychloroquine, sulfasalazine, and leflunomide. Methotrexate monotherapy is also recommended over monotherapy with biologics (TNFi, IL-6 inhibitors, abatacept) or JAK inhibitors. For individuals taking maximally tolerated doses MTX who are not at target, the addition of a biologic or JAK inhibitor is recommended. Non-TNFi biologics or JAK inhibitors are conditionally recommended over TNFi in individuals with heart failure.

ANCA-associated vasculitis: Antineutrophil cytoplasmic antibody (ANCA)- associated vasculitis AAV is a collection of relatively rare autoimmune diseases of unknown causes, characterized by inflammatory cell infiltration causing necrosis of blood vessels. The clinical presentation of disease can vary, ranging from a skin rash to fulminant multisystem disease. Three subtypes of the disease include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and Eosinophilic granulomatosis with polyangiitis (EGPA-previously known as Churg-Strauss). Rituximab, in combination with glucocorticoids, is indicated for the treatment of patients age 2 and above with GPA or MPA. The American College of Rheumatology (ACR)/ Vasculitis Foundation guidelines recommend rituximab for remission induction for active, severe disease and for remission maintenance in those that have entered remission after treatment with cyclophosphamide or rituximab.

Pemphigus vulgaris and other autoimmune blistering skin diseases: Pemphigus is a life-threatening autoimmune blistering disease affecting the skin and mucosa and is comprised of three major forms characterized by autoantibodies directed against epidermal cell junctions: pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus (PNP). Rituximab (Rituxan) is FDA approved for moderate to severe pemphigus vulgaris and there is literature to support its use as first-line therapy and in treatment refractory disease. In addition, there

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are case series and retrospective comparative studies that support the use of rituximab in refractory pemphigoid disease [bullous pemphigoid and mucous membrane pemphigoid (such as cicatricial pemphigoid and epidermolysis bullosa acquisita)].

Myasthenia Gravis (MG): MG is a common disorder of neuromuscular transmission characterized by a variable combination of weakness in ocular, bulbar, limb, and respiratory muscles. Treatment strategies include symptomatic therapy (with anticholinesterase agents such as pyridostigmine), chronic immunotherapy with steroids or other immunosuppressive drugs (such as azathioprine, cyclosporine, or methotrexate), rapid immunotherapy (with plasmapheresis or IVIG), and/or surgical treatment. The Myasthenia Gravis Foundation of America (MGFA) international consensus guidelines recommend immunosuppressive drugs (such as azathioprine or cyclosporine) and/or corticosteroids for individuals who have not met treatment goals after an adequate trial of pyridostigmine. Rapid immunotherapy (with IVIG or plasmapheresis), cyclophosphamide, or rituximab may be considered for refractory MG. Rituximab can be considered in those who have an unsatisfactory response to initial immunotherapy, or in those who do not tolerate other immunosuppressive agents.

Antibody-Mediated Solid Organ Transplant Rejection: Antibody-mediated rejection is caused by anti-donor-specific antibodies, mostly anti-HLA antibodies. Treatment for acute antibody-mediated rejection generally consists of IVIG and rituximab, with or without plasma exchange. Chronic AMR has remained a significant problem with a lack of standardized treatment and limited therapeutic options. Literature and guideline recommendations (KDIGO 2009, ISHLT 2010) support rituximab as a potential treatment option for antibody-mediated rejection. Based on guideline recommendations, available literature, limited alternative treatment options, and views of relevant medical specialists, the use of rituximab may be considered for antibody-mediated rejection.

***Rituxan Hycela is not indicated for the treatment of non-oncology conditions.

- **Oncology-Related Indications**

CD20 plays a crucial role in the early stages of cell cycle activation and differentiation, possibly also serving as a calcium ion channel. Importantly, it remains anchored to the cell surface and does not internalize upon antibody attachment. There is no detectable free CD20 antigen circulating in the body. The mechanism of rituximab anti-cancer action likely involves two main processes: (1) Rituximab's Fab domain binding to CD20 on B lymphocytes, which can lead to the destruction of B cells, potentially through immune effector functions activated by the Fc domain. This destruction may occur through complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC); (2) Additionally, the antibody has demonstrated the ability to trigger apoptosis in the DHL-4 human B-cell lymphoma line.

The reference product Rituxan (rituximab) is FDA approved for the treatment of CD20-positive Non-hodgkin's lymphomas (NHL) including relapsed/refractory low-grade or follicular NHL, previously untreated follicular lymphoma, non-progressing low-grade NHL, and previously untreated diffuse large B-cell lymphoma. NCCN defines low-grade lymphomas as follicular lymphoma and marginal zone lymphoma which includes Malt

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lymphomas and nodal/splenic type. Rituxan is also FDA approved to treat chronic lymphocytic leukemia (CLL) in combination with fludarabine and cyclophosphamide and for pediatric patients aged 6 months and older with previously untreated, advanced stage, CD20-positive diffuse large B-cell Lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL), or mature B-cell acute leukemia (B-AL) in combination with chemotherapy. Three biosimilars to Rituxan, Truxima (rituximab-abbs), Ruxience (rituximab-pvvr), and Riabni (rituximab-arrx) have been approved by the FDA.

Biosimilar products

Biosimilar products must be highly similar to the reference product and there must be no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product. Biosimilars must utilize the same mechanism of action (MOA), route of administration, dosage form and strength as the reference product; and the indications proposed must have been previously approved for the reference product. The potential exists for a biosimilar product to be approved for one or more indications for which the reference product is licensed based on extrapolation of data intended to demonstrate biosimilarity in one indication. Sufficient scientific justification for extrapolating data is necessary for FDA approval. Factors and issues that should be considered for extrapolation include the MOA for each indication, the pharmacokinetics, bio- distribution, and immunogenicity of the product in different patient populations, and differences in expected toxicities in each indication and patient population.

Truxima (rituximab-abbs) was originally approved as the first rituximab biosimilar with FDA approval for the same oncologic indications as Rituxan. However, now the reference product Rituxan has an additional oncologic indication for pediatric patients aged 6 months and older with previously untreated, advanced stage, CD20-positive diffuse large B-cell Lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL), or mature B-cell acute leukemia (B- AL) in combination with chemotherapy. Clinical review of Truxima included two clinical studies that compared Truxima with Rituxan in the oncology setting. Demonstration of biosimilarity was also based on a third study (Shim 2019), a randomized, controlled, double-blind, 3-arm study of Truxima, US-Rituxan, and EU-approve MabThera in patients with rheumatoid arthritis (RA). This clinical data in RA was also used to support the clinical scenario where non-treatment naïve patients may undergo a single transition to Truxima based on the similar safety, efficacy, and immunogenicity profile between patients undergoing a single transition from Rituxan or MabThera to Truxima as compared to those who continued treatment with comparator product. Subsequently, Truxima was approved for RA and GPA/MPA. Both Ruxience and Riabni were granted FDA approval for the same oncologic indications as the reference product at the time in addition to GPA/MPA in adults only. Both subsequently were approved for RA. Now the reference product Rituxan has an additional oncologic indication for pediatric patients aged 6 months and older with DLBCL, BL, BLL, or B-AL. Approval for Ruxience was, in part, based on a phase 3, randomized double-blind study of Ruxience versus MabThera in patients with low tumor burden follicular lymphoma (NCT02213263). Ruxience has also been studied in rheumatoid arthritis (Cohen 2018). This was an extension study from a previous 3-arm pharmacokinetic study involving Ruxience, Rituxan, and MabThera. Subjects who received reference products Rituxan or MabThera were randomized to continue treatment or switch to Ruxience for one treatment; and then all subjects continued with Ruxience. This study also demonstrated tolerability and acceptable safety with a single transition from reference to biosimilar. Riabni

approval data package included a study in follicular lymphoma and a study in rheumatoid arthritis. Subjects with active RA were randomized to Riabni, MapThera, or Rituxan; and subjects receiving Rituxan were transitioned to Riabni after the first two doses. There was no statistical difference on disease activity score change from baseline between patients treated with Riabni or a rituximab product (Burmester 2020). Based on the totality of submitted data, the FDA concluded that these biosimilar agents are highly similar to Rituxan; there are no clinically meaningful differences between them and Rituxan; and that there is justification to support licensure for the proposed indications. Therefore, as biosimilars have demonstrated biosimilarity to Rituxan for FDA indications, it is reasonable for biosimilarity to be extrapolated to off-label indications as well.

Rituximab products are used in defined treatment periods when used in oncologic indications. The package insert recommends that rituximab be used up to 2 years where it is indicated as maintenance therapy. As treatment periods are definite, NCCN notes that the biosimilar may be substituted for the reference product at the initiation of a course of treatment. Additionally, no biosimilar rituximab agent is approved as interchangeable, so the patient should remain on the same product that was used to initiate treatment during a single course of therapy. At this time, there is insufficient evidence for efficacy and safety of switching between the reference and biosimilar product in the treatment of oncologic indications.

Rituxan, Truxima, Riabni, and Ruxience have black box warnings for fatal infusion reactions, severe mucocutaneous reactions, hepatitis B virus (HBV) reactivation, and progressive multifocal leukoencephalopathy (PML). Rituximab administration can result in serious, including fatal, infusion reactions and deaths within 24 hours of infusion have occurred, most in association with the first infusion. Monitor individuals closely; discontinue rituximab infusion for severe reactions and provide medical treatment for grade 3 or 4 reactions. Severe, including fatal, mucocutaneous reactions can occur. HBV reactivation can occur, in some cases resulting in fulminant hepatitis, hepatic failure, and death. Screen all individuals for HBV infection before treatment initiation and monitor during and after treatment with rituximab. Discontinue rituximab and concomitant medications in the event of HBV reactivation. PML, including fatal PML, can occur.

Approved Indications

Summary of FDA-approved and off-label non-oncologic indications for rituximab agents

	Rituxan (rituximab)	Truxima (rituximab- abbs)	Ruxience (rituximab-pvvr)	Riabni (rituximab-arrx)
Rheumatoid Arthritis	X	X	X	X
Granulomatosis with Polyangiitis and Microscopic Polyangiitis	X	X	X	X
Pemphigus vulgaris	X	Y^	Y^	Y^
Acquired hemophilia or inhibitors in hemophilia	Y	Y^	Y^	Y^

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Autoimmune hemolytic anemia	Y	Y^	Y^	Y^
Cryoglobulinemia, primary Sjogren Syndrome, or systemic lupus erythematosus	Y	Y^	Y^	Y^
Graft-Versus-Host Disease	Y	Y^	Y^	Y^
Hepatitis C virus infection-related glomerulonephritis	Y	Y^	Y^	Y^
Immunoglobulin G4-related disease	Y	Y^	Y^	Y^
Relapsing multiple sclerosis	Y	Y^	Y^	Y^
Neuromyelitis optica	Y	Y^	Y^	Y^

X = FDA approved indication; Y = *Off-label use*; *Y^= Off-label indication based on clinical judgement of biosimilarity by 1Q 2021 P&T committee*

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	Rituxan (rituximab)	Truxima (rituximab-abbs)	Ruxience (rituximab-pvvr)	Riabni (rituximab-arrx)
Follicular Lymphoma	X	X	X	X
Gastric/nongastric malt Lymphoma	X/NCCN*	X/NCCN*	X/NCCN*	X/NCCN*
Nodal/Splenic Marginal Zone Lymphoma	X/NCCN*	X/NCCN*	X/NCCN*	X/NCCN*
Extranodal Marginal Zone Lymphoma	Y/NCCN	Y/NCCN	Y/NCCN	Y/NCCN
Histologic transformation of Indolent lymphoma to DLBCL	Y	Y	Y	Y
Post-transplant lymphoproliferative disorders	Y	Y	Y	Y
Castleman's disease	Y	Y	Y	Y
Mantle Cell lymphoma	Y	Y	Y	Y
DLBCL	X	X	X	X
High-Grade B-Cell lymphomas	Y	Y	Y	Y
Burkitt Lymphoma	X	Y	Y	Y
HIV-related B-cell Lymphomas	Y	Y	Y	Y
Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma	X	X	X	X
Primary Cutaneous B-Cell Lymphomas	Y	Y	Y	Y
Pediatric Aggressive Mature B- Cell Lymphomas	X	Y	Y	Y
Acute lymphoblastic Leukemia	Y	Y	Y	Y
Primary CNS Lymphoma	Y	Y	Y	Y
Leptomeningeal Metastases	Y	Y	Y	Y
Hairy Cell Leukemia	Y	Y	Y	Y
Hematopoietic Cell Transplantation	Y	Y	Y	Y
Histiocytic Neoplasms	Y	Y	Y	Y
Hodgkin Lymphoma	Y	Y	Y	Y
Waldenstrom Macroglobulinemia/	Y	Y	Y	Y

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Lymphoplasmacytic Lymphoma				

X= FDA approved use; Y= Off-label use; Y^= Off-label indication based on clinical judgement of biosimilarity by 3Q 2021 P&T committee. *NCCN defines low grade non-hodgkins lymphomas as MALT lymphoma and marginal zone lymphoma

Note: When a rituximab agent is deemed approvable based on the clinical criteria above, the benefit plan may have additional criteria requiring the use of a preferred agent or agents.

Rituxan Hycela®

Other Uses

Based on the results from published data in the peer-reviewed medical literature, rituximab is also used to treat additional non-oncologic indications that are not currently approved by the FDA. Supporting literature includes guideline recommendations, randomized controlled trials, retrospective studies, case series, case reports, and specialty consensus opinion. International Acquired Hemophilia A guidelines suggest adding rituximab to first-line therapy in individuals with inhibitor titer >20 BU, and as a second-line agent in refractory individuals (Tiede 2020).

Rituximab is also used as treatment for autoimmune hemolytic anemia, including warm autoimmune hemolytic anemia and cold agglutinin disease (Jager 2020). It has also been studied in autoimmune diseases such as cryoglobulinemia, sjogren syndrome, and systemic lupus erythematosus that are refractory to standard treatment (Fanouriakis 2019, Ramos-Casals 2020) and as treatment for refractory Graft Versus Host Disease (NCCN 2A). KDIGO guidelines review the use of rituximab in Hepatitis C virus infection-related glomerulonephritis, pediatric nephrotic syndrome, membranous nephropathy, and renal transplant (pre- and post- transplant). The American Academy of Neurology (AAN) guidelines recommend disease modifying therapies (DMTs), such as rituximab, in individuals with relapsing forms of MS with recent clinical relapses or MRI activity. The American Society of Hematology 2019 guidelines suggest rituximab for initial or second-line treatment of Immune thrombocytopenia (ITP), also called idiopathic thrombocytopenic purpura or immune thrombocytopenic purpura. The International Society on Thrombosis and Haemostasis (ISTH) Guidelines for treatment of thrombotic thrombocytopenic purpura recommend rituximab for treatment of acute events and relapses, and as prophylaxis for individuals who are in remission.

Consensus recommendations for the management of autoimmune encephalitis suggest rituximab for disease refractory to initial therapy with immunoglobulin or plasma exchange therapy (Zuliani 2019, Abboud 2021).

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Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

For a comprehensive list of covered ICD-10, including oncology-related indications, please see Billing and Coding: Rituximab.

HCPCS	Description
J9312	Injection, rituximab, 10 mg [Rituxan]
Q5115	Injection, rituximab-abbs, biosimilar, (Truxima), 10 mg
Q5119	Injection, rituximab-pvvr, biosimilar, (Ruxience), 10 mg
Q5123	Injection, rituximab-arrx, biosimilar, [Riabni], 10 mg
J9311	Injection, rituximab 10 mg and hyaluronidase, [Rituxan Hycela]

ICD-10	Description
B17.10-B17.11	Acute hepatitis C
B18.2	Chronic viral hepatitis C
B19.20-B19.21	Unspecified viral hepatitis C
D59.0-D59.19	Drug-induced, other autoimmune hemolytic anemias
D68.311	Acquired hemophilia
D69.3	Immune thrombocytopenic purpura (idiopathic thrombocytopenic purpura)
D89.1	Cryoglobulinemia
D89.810-D89.89	Other specified disorders involving the immune mechanism, not elsewhere classified [Graft-versus-host disease, ALPS]
G04.81	Other encephalitis and encephalomyelitis
G35	Multiple sclerosis
G36.0	Neuromyelitis optica [Devic]
G70.00-G70.01	Myasthenia gravis
L10.0-L10.9	Pemphigus
L12.0-L12.9	Pemphigoid (epidermolysis bullosa)
M05.00-M05.9	Rheumatoid arthritis with rheumatoid factor
M06.00-M06.09	Rheumatoid arthritis without rheumatoid factor
M06.80-M06.9	Other specified rheumatoid arthritis and rheumatoid arthritis, unspecified
M31.10	Thrombotic microangiopathy (thrombotic thrombocytopenic purpura)
M31.30-M31.31	Wegener's granulomatosis

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M31.7	Microscopic polyangiitis
M32.0-M32.9	Systemic lupus erythematosus (SLE)
M35.00-M35.09	Sicca syndrome (Sjögren)
M35.5	Multifocal fibrosclerosis [when specified as immunoglobulin G4-related disease]
M35.9	Systemic involvement of connective tissue, unspecified [when specified as immunoglobulin G4-related disease]
N01.0-N01.9	Rapidly progressive nephritic syndrome
N04.0-N04.9	Nephrotic syndrome
N06.0-N06.9	Isolated proteinuria with specified morphological lesion
N08	Glomerular disorders in diseases classified elsewhere
N18.1-N18.9	Chronic kidney disease (CKD)
Q81.0-Q81.9	Epidermolysis bullosa
T86.00-T86.99	Complications of transplanted organs and tissue
Z48.22	Encounter for aftercare following kidney transplant
Z94.0	Kidney transplant status

Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Rituxan (rituximab); Riabni (rituximab-arrx); Ruxience (rituximab-pvvr); Truxima (rituximab-abbs); Rituxan Hycela® (rituximab and hyaluronidase)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

For Non-Oncology Related Indications (Rituxan Hycela is not indicated for patients with non-oncology conditions)

i. Rheumatoid arthritis (RA) when each of the following criteria are met:
   A. Individual is 18 years of age or older with moderate to severe RA; **AND**
   B. Individual has had an inadequate response to methotrexate titrated to maximally tolerated dose (ACR 2021); **OR**
   C. If methotrexate is not tolerated or contraindicated, individual has had an inadequate response to, is intolerant of, or has a contraindication to other conventional therapy [sulfasalazine, leflunomide, or hydroxychloroquine]; **AND**

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D. Individual had an inadequate response, is intolerant of, or has a contraindication to one or more tumor necrosis factor (TNF) antagonist therapies;

OR

ii. Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA) when each of the following criteria are met:
   A. Individual is 2 years of age or older with Granulomatosis with Polyangiitis (GPA) and MPA; **AND**
   B. Individual is using concomitantly with glucocorticoids with or without avacopan for induction treatment;
   OR
   C. Individual is using as follow up treatment after achieving disease control with induction treatment;

OR

iii. Autoimmune blistering skin diseases (such as but not limited to pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, cicatricial pemphigoid, epidermolysis bullosa acquisita and paraneoplastic pemphigus) (Ahmed 2016, Maley 2016) when either of the following criteria are met:
   A. As first-line treatment in adults with moderate to severe pemphigus vulgaris; **OR**
   B. Disease is treatment-refractory;

OR

iv. Acquired hemophilia or acquired inhibitors in individuals with hemophilia when used in combination with corticosteroids or in individuals who have had an inadequate response, are intolerant of, or have a contraindication to corticosteroid and cytotoxic therapy (Collins 2009, Tiede 2020);

OR

v. Autoimmune hemolytic anemia (Birgens 2013, Michel 2017, DP B IIb);

OR

vi. Cryoglobulinemia, primary Sjogren Syndrome, or systemic lupus erythematosus refractory to standard therapy (Ramos 2009, DP B IIb) including:
   A. Corticosteroids; **AND**
   B. Two (2) or more immunosuppressive agents (such as but not limited to azathioprine, cyclosporine, methotrexate, or hydroxychloroquine);

OR

vii. Steroid-refractory Graft-Versus-Host Disease (Cutler 2006, NCCN 2A, DP B IIb);

OR

viii. Hepatitis C virus infection-related glomerulonephritis in individuals with cryoglobulinemic flare, rapidly progressing glomerulonephritis, or nephrotic syndrome (KDIGO 2022);

OR

ix. Immunoglobulin G4-related disease when any of the following criteria are met (Khosroshahi 2015):
   A. Failure to respond to prednisone or other corticosteroid agents; **OR**

B. Unable to tolerate tapering of prednisone or other corticosteroid agents; **OR**
C. Has a contraindication to prednisone or other corticosteroid agents;

OR

x. Relapsing Multiple sclerosis (AAN 2018, DP B IIb);

OR

xi. Neuromyelitis optica (Nikoo 2017, Tahara 2020);

OR

xii. Pediatric nephrotic syndrome when each of the following criteria are met (KDIGO 2021, DP B IIb):
A. Individual is 18 years of age or younger; **AND**
B. Individual has steroid-dependent, relapsing disease; **AND**
C. Individual has had an inadequate response to, is intolerant of, or has a contraindication to corticosteroids or immunosuppressive agents (such as but not limited to cyclosporine, cyclophosphamide, or mycophenolate);

OR

xiii. Membranous Nephropathy (MN) when each of the following criteria are met (KDIGO 2021):
A. Individual has moderate to high risk MN as shown by one of the following:
B. Individual has proteinuria > 3.5 g/d and proteinuria has not decreased > 50% after 6 months of conservative therapy with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs); **OR**
C. Individual has an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2;

OR

xiv. Renal transplant setting for either of the following indications (Vo 2010, KDIGO 2020):
A. Pre-transplant to suppress panel reactive anti-human leukocyte antigens (HLA) antibodies in individuals with high panel reactive antibody (PRA or cPRA [corrected PRA]) levels to HLAs **or** in individuals with a history of high levels of donor-specific antibodies (DSAs); **OR**
B. Post-transplant in individuals with acute rejection who had received rituximab treatment pre-transplant;

OR

xv. Antibody-mediated solid organ transplant rejection (KDIGO 2009, ISHLT 2010);

OR

xvi. Thrombocytopenic purpura, immune or idiopathic (ITP) (ASH 2019);

OR

xvii. Immune mediated thrombotic thrombocytopenic purpura (TTP) when each of the following criteria are met (ISTH 2020):
A. TTP is confirmed by severely reduced baseline activity of ADAMTS 13 (less than 10%), with the presence of an ADAMTS 13 inhibitor or anti-ADAMTS13 IgG; **AND**
B. Individual is using in combination with plasma exchange therapy and glucocorticoids for treatment of acute event or relapse;
OR
C. Individual is in remission and using for prevention of relapse;

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OR

xviii. Myasthenia gravis when the following criteria are met (MGFA 2020, DP B I):
- A. Individual is 18 years of age or older with myasthenia gravis; **AND**
- B. Individual has had an inadequate response to, is intolerant of, or has a contraindication to two or more immunosuppressive drug agents (such as azathioprine, cyclosporine, or methotrexate).

OR

xix. Immune-mediated encephalitis, including paraneoplastic and autoimmune encephalitis when the following criteria are met (Zuliani 2019, Lancaster 2016):
- A. Diagnosis is confirmed by detection of a specific autoantibody associated with encephalitis [including but not limited to: NMDAR, LGI1, Caspr2, AMPAR, GABA-A or GABA-B receptor, IgLON5, DPPX, GlyR, mGluR1, mGluR2, mGluR5, Neurexin 3-alpha, or dopamine-2 receptor (D2R)]; **AND**
- B. Individual has had an inadequate response to, is intolerant of, or has a contraindication to first line agent(s) including immunoglobulin therapy *or* plasma exchange;

OR

xx. Immunotherapy-related toxicities including (NCCN 2A):
- A. Moderate, severe, or life-threatening bullous dermatitis; **OR**
- B. Moderate, severe, or life-threatening myositis for significant dysphagia, life-threatening situations, or cases refractory to corticosteroids; **OR**
- C. Severe myasthenia gravis refractory to prior therapy; **OR**
- D. Encephalitis refractory to prior therapy in individuals positive for autoimmune encephalopathy antibody.

For Oncology Related Indications:

- Rituximab agents may be approved for an indication listed in the table: *FDA-approved and off-label oncologic indications for rituximab agents in the Services Description section above*. When a rituximab agent is deemed approvable based on the clinical criteria above, MMM may have additional criteria requiring the use of a preferred agent or agents. Documentation required for approval may include:
  - Medical records, labs, imaging studies, or any other documentation that substantiate the medical need for the use of Rituximab by clearly indicating the diagnoses, classification (e.g. lymphoma type), and staging.
  - All prior therapy and the patient's response to that therapy.
- Rituximab Hycela® may be approved if the following criteria are met:
  - i. The patient is using for a Rituximab oncologic indication listed in the table: *FDA-approved and off-label oncologic indications for rituximab agents in the Services Description section above*; **AND**

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ii. Patient has received at least one full dose of a rituximab product by intravenous infusion and has not experienced serious adverse reactions, **AND**

iii. The patient has an inadequate response, contraindication, or intolerance to a preferred i.v. rituximab agent.

B. Criteria For Continuation of Therapy

i. MMM considers continuation of rituximab agents (including Rituxan Hycela®) medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of unacceptable toxicity (oncology-related indications), there has been adequate response to therapy (non-oncology related indications), and the recommended duration of therapy has not been exceeded. The following information should be submitted for reauthorization:

A. A current note of the prescriber documenting the patient's response to treatment showing adequate response to therapy (non-oncology related indications).

B. Current imaging studies and/or other objective measures, if appropriate depending on the indication, showing adequate response to therapy when compared with previous results.

C. Authorization Duration

i. Initial Approval Duration: Per request, up to 6 months (for the maximum duration of treatment as described in the product labeling information or approved compendia)

ii. Reauthorization Approval Duration: Per request, up to 6 months (for the maximum duration of treatment as described in the product labeling information or approved compendia)

D. **Conditions Not Covered**

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Requests for Rituxan (rituximab), Riabni (rituximab-arrx), Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may not be approved when the above criteria (Section A: Criteria for Initial Approval) are not met and for all other indications.

ii. Requests for Rituxan Hycela for a non-oncology related condition.

Limits or Restrictions

A. Therapeutic Alternatives

This medical policy may be subject to Step Therapy. Please refer to the document published on the MMM Website: https://www.mmm-pr.com/planes-medicos/formulario-medicamentos

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B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

- **Rituximab for Non-Oncologic Indications Quantity Limit**

Drug	Limit Per Indication
Rituxan (rituximab) 100 mg, 500 mg vial; Riabni (rituximab-arrx) 100 mg, 500 mg vial; Ruxience (rituximab- pvvr) 100 mg, 500 mg vial; Truxima (rituximab-abbs) 100 mg, 500 mg vial	**Rheumatoid arthritis (RA):** 1000 mg on days 1 and 15; repeated as frequent as every 16 weeks **Pemphigus Vulgaris & other autoimmune blistering skin diseases; maintenance**: 500 mg as frequently as every 16 weeks* **Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) maintenance:** 500 mg every 6 months† **Myasthenia Gravis**: 375 mg/m^2 monthly (DP)^ **Autoimmune Hemolytic Anemia:** 375 mg/m^2 weekly for 4 weeks (DP) **Immune Thrombocytopenia (ITP):** 375 mg/m^2 weekly for up to 4 weeks (DP) **Primary Sjogren's Syndrome:** 1000 mg on days 1 and 15 (2000 mg total) (DP)
Exclusion	
*For initiation of therapy, may approve two 1000mg doses separated by 2 weeks. May also approve one 1000 mg infusion upon relapse †For induction treatment, may approve 375 mg/m^2 weekly for 4 weeks (Label) or 1000 mg on days 1 and 15 (DP). After induction (at least 16 weeks after rituximab induction or within 4 weeks after achieving disease control from induction with other standard of care immunosuppressants), may approve two 500mg infusions separated by 2 weeks followed by maintenance therapy. ^May approve 375 mg/m^2 weekly for 4 weeks when initiating therapy or as clinically indicated upon relapse.	

- **Rituximab for FDA Approved Oncologic Indications Quantity Limit (according to FDA approved labeling)**

Indication	Dose	Duration of Treatment
Non-Hodgkin Lymphoma (NHL)		
Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL	375 mg/m^2 once weekly	4 or 8 doses

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Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL	375 mg/m^2 once weekly	4 doses
Previously Untreated, Follicular, CD20-Positive, B-Cell NHL (1st line follicular NHL)	First line therapy in combination with chemotherapy: 375 mg/m^2 once weekly	Up to 8 doses
	As single agent following complete or partial response to first line: 375 mg/m^2 every 8 weeks	For 12 doses
Non-progressing, Low-Grade, CD20-Positive, B-Cell NHL, after first-line CVP chemotherapy	375 mg/m^2 once weekly for 4 doses at 6-month interval (following completion of CVP chemotherapy)	16 doses
Diffuse Large B-Cell NHL (DLBCL)	375 mg/m^2 on Day 1 of each cycle of chemotherapy	Up to 8 infusions
Component of Zevalina® for treatment of NHL	250 mg/m^2	Up to 4 doses (Days 1, 7, 8, 9)
Chronic Lymphocytic Leukemia		
Chronic Lymphocytic Leukemia (CLL)	The day prior to the initiation of FC chemotherapy: 375 mg/m^2	1 dose
	Day 1 of cycles 2-6 (every 28 days): 500 mg/m2	5 doses (every 28 days)

FC: fludarabine and cyclophosphamide; CVP: cyclophosphamide, vincristine, and prednisone

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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Policy Inception	New Medical Policy creation. Policy reviewed and approved by P&T Committee.	10/30/2023	11/30/2023
Select Review	• Add new rituximab formulation: Rituxan Hycela (rituximab and hyaluronidase). • Update Approved Indications. Coding Reviewed: Added J9311 for Rituxan Hycela.	3/25/2024	6/28/2024
Select Review	• Update statement for criteria for initial approval: Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met all approval criteria.	4/18/2024	6/28/2024

Revised: 10/24/2023