Policy Number	**RX502.030**
Policy Effective Date	**01/01/2026**

Rituximab and Biosimilars for Non-Oncologic Indications

Table of Contents

Related Policies (if applicable)
RX502.061: Oncology Medications

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Medical Benefit Therapeutic Alternatives

Certain prescription drugs administered by a health care provider in a clinical or professional setting have therapeutic equivalents or alternatives. Benefits may be limited to certain therapeutic equivalents or alternatives unless a coverage exception is granted. Members and their providers may visit the plan website for more information or may call the number on the member's ID card for further assistance.

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as

safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

NOTE 1: Refer to RX502.061 Oncology Medications for oncologic indications of rituximab (Rituxan), rituximab biosimilars and rituximab/hyaluronidase human (Rituxan Hycela).

NOTE 2: See the Appendix for exception criteria for medications in this class. The Appendix is not applicable to plans regulated by the Illinois Department of Insurance or Medicare or Medicaid plans.

Rituximab (Rituxan® and the biosimilars rituximab-abbs [Truxima®], rituximab-pvvr [Ruxience®], and rituximab-arrx [Riabni®]) **may be considered medically necessary** for the following U.S. Food and Drug Administration (FDA) labeled indications:

- In combination with methotrexate (if no contraindication or intolerance to methotrexate exists) for patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to either methotrexate OR a tumor necrosing factor (TNF) antagonist;
- Granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis) and microscopic polyangiitis (MPA) in **adult and pediatric patients 2 years of age and older** in combination with glucocorticoids;
- Pemphigus vulgaris, moderate to severe in adult patients.

Rituximab (Rituxan® and the biosimilars rituximab-abbs [Truxima®], rituximab-pvvr [Ruxience®], and rituximab-arrx [Riabni®]) **may be considered medically necessary** for the following non-FDA labeled indications:

- Autoimmune hemolytic anemia (AIHA) as listed below:
  - Warm AIHA in glucocorticoid-refractory or glucocorticoid-dependent individuals,
  - Cold agglutination syndrome;
- Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis):
  - First-line treatment in combination with corticosteroids for patients with severe (organ-threatening) disease,
  - Add-on therapy for treatment-refractory disease;
- Cryoglobulinemic vasculitis, as add-on therapy for patients with hepatitis C virus (HCV) associated disease who have:

    - Active disease resistant to anti-viral drugs, or
    - Severe or life-threatening cryoglobulinemic vasculitis;
- Dermatomyositis, refractory;
- In patients with factor inhibitor related acquired hemophilia who are refractory to conventional first-line treatments (e.g., immune tolerance induction, corticosteroids with or without cyclophosphamide), preferably as add-on therapy;
- Graft-versus-host disease that is chronic and steroid-refractory;
- Idiopathic membranous nephropathy;
- Lupus nephritis, as add-on therapy for patients who are refractory to at least one standard first-line treatment regimen;
- Minimal change disease (MCD) [also known as lipoid nephrosis or nil disease], refractory AND steroid-dependent or steroid-resistant;
- Myasthenia gravis, refractory;
- Neuromyelitis optica;
- Ocular cicatricial pemphigoid, refractory;
- Primary Sjögren's syndrome that is refractory to glucocorticoids and other immunosuppressive agents;
- Renal transplant candidates before transplantation, sensitized for inhibition of antibody production;
- Relapsing-remitting multiple sclerosis;
- Systemic lupus erythematosus, refractory to immunosuppressive therapy;
- Systemic sclerosis (scleroderma) in patients refractory to first-line treatment;
- Thrombocytopenic purpura (i.e., immune, thrombotic [TTP] or idiopathic [ITP]).

All other uses of rituximab (Rituxan®) and rituximab biosimilars (i.e., Truxima®, Ruxience® and Riabni®) not specified above **are considered experimental, investigational and/or unproven.**

Policy Guidelines

Rituximab should be administered by a health care professional with appropriate medical support to manage severe and potentially fatal infusion reactions.

Description

Rituximab
Rituximab (Rituxan®) is a chimeric murine-human monoclonal antibody directed against the CD20 surface antigen, which is expressed on pre-B and mature B lymphocytes. Rituximab induces lyses of normal and malignant CD20-expressing B cells; possible mechanisms of cell lysis induce complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. (5)

B cells are thought to play a role in the pathogenesis of rheumatoid arthritis and other autoimmune diseases by producing auto-antibodies and proinflammatory cytokines, and by activating T lymphocytes. (5) Rituximab reduces the number of B cells in the peripheral blood and in lymphoid tissues, thereby interrupting pathogenic processes of autoimmune diseases.

Rituximab is infused intravenously.

Adverse Events

Rituximab carries the following Boxed warnings: (1)

- Fatal infusion reactions within 24 hours of rituximab infusion; approximately 80% of fatal reactions occurred with the first infusion
- Severe mucocutaneous reactions, some with fatal outcomes
- Hepatitis B virus reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death
- Progressive multifocal leukoencephalopathy resulting in death

Labeled warnings and precautions include:

- Tumor lysis syndrome (for patients with hematologic malignancies)
- Infections
- Cardiac arrhythmias and angina
- Renal toxicity
- Bowel obstruction and perforation
- Not administering live virus vaccines before or during rituximab therapy
- Cytopenias
- Embryo-fetal toxicity
- Limited data on concomitant use with other biologic agents and disease-modifying antirheumatic drugs other than methotrexate in rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and pemphigus vulgaris
- Limited data on use in rheumatoid arthritis patients who have not had prior inadequate response to tumor necrosis factor antagonists

Regulatory Status

For non-oncologic indications, the U.S. Food and Drug Administration (FDA) provided approval for rituximab and its biosimilars as indicated in Table 1. (6-10)

Table 1. FDA Approval for Non-Oncologic Indications

Drug	Date Approved	Indication
Rituxan®	Feb. 28, 2006	Treatment of moderate-to-severe rheumatoid arthritis
	April 19, 2011	Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) in combination with glucocorticoids
	June 7, 2018	Pemphigus vulgaris

	Sept. 27, 2019	Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) in children
Ruxience®	July 23, 2019	As a biosimilar to Rituxan
Truxima®	Nov. 28, 2018	As a biosimilar to Rituxan
Riabni®	Dec. 17, 2020	As a biosimilar to Rituxan
	June 3, 2022	Treatment of moderate-to-severe rheumatoid arthritis

NOTE 3: Refer to RX502.061 Oncology Medications for oncologic indications of rituximab (Rituxan) and biosimilars.

Rationale

This policy is based on the U.S. Food and Drug Administration (FDA) labeled indications for rituximab (Rituxan® and the biosimilars rituximab-abbs [Truxima®], rituximab-pvvr [Ruxience®], and rituximab-arrx [Riabni®]), as well as research of the compendia for non-labeled indications.

FDA LABELED INDICATIONS
Rheumatoid Arthritis (1-4)
Reducing the Signs and Symptoms: Initial and Re-Treatment Courses
The efficacy and safety of Rituxan were evaluated in two randomized, double-blind, placebo-controlled studies of adult patients with moderately to severely active rheumatoid arthritis (RA) who had a prior inadequate response to at least one tumor necrosing factor (TNF) inhibitor. Patients were 18 years of age or older, diagnosed with active RA according to American College of Rheumatology (ACR) criteria, and had at least 8 swollen and 8 tender joints.

In RA Study 1 (NCT00468546), patients were randomized to receive either Rituxan 2 x 1000 mg + methotrexate (MTX) or placebo + MTX for 24 weeks. Further courses of Rituxan 2 x 1000 mg + MTX were administered in an open label extension study at a frequency determined by clinical evaluation, but no sooner than 16 weeks after the preceding course of Rituxan. In addition to the intravenous premedication, glucocorticoids were administered orally on a tapering schedule from baseline through Day 14. The proportions of patients achieving ACR 20, 50, and 70 responses at week 24 of the placebo-controlled period are shown in Table 2.

In RA Study 2 (NCT00266227), all patients received the first course of Rituxan 2 x 1000 mg + MTX. Patients who experienced ongoing disease activity were randomized to receive a second course of either Rituxan 2 x 1000 mg + MTX or placebo + MTX, the majority between weeks 24–28. The proportions of patients achieving ACR 20, 50, and 70 responses at week 24, before the re-treatment course, and at week 48, after retreatment, are shown in Table 2.

Table 2. ACR Responses in RA Study 1 and RA Study 2 (Percent of Patients) (Modified Intent-to-Treat Population)

Inadequate Response to TNF Antagonists

Study 1 24 Week Placebo-Controlled (Week 24)				Study 2 Placebo-Controlled Retreatment (Week 24 and Week 48)			
Response	**Placebo + MTX n=201**	**Rituxan + MTX n=298**	**Treatment Difference (Rituxan-Placebo)[c] (95% CI)**	**Response**	**Placebo + MTX Retreatment n=157**	**Rituxan + MTX Retreatment n=318**	**Treatment Difference (Rituxan-Placebo)[a,b,c] (95% CI)**
ACR20				**ACR20**			
Week 24	18%	51%	33% (26%, 41%)	**Week 24**	48%	45%	NA
				Week 48	45%	54%	11% (2%, 20%)
ACR50				**ACR50**			
Week 24	5%	27%	21% (15%, 27%)	**Week 24**	27%	21%	NA
				Week 48	26%	29%	4% (-4%, 13%)
ACR70				**ACR70**			
Week 24	1%	12%	11% (7%, 15%)	**Week 24**	11%	8%	NA
				Week 48	13%	14%	1% (-5%, 8%)

ACR: American College of Rheumatology; CI: confidence interval; MTX: methotrexate; NA: not applicable; RA: rheumatoid arthritis; TNF: tumor necrosing factor.

[a] In RA Study 2, all patients received a first course of Rituxan 2 x 1000 mg. Patients who experienced ongoing disease activity were randomized to receive a second course of either Rituxan 2 x 1000 mg + MTX or placebo + MTX at or after week 24.

[b] Since all patients received a first course of Rituxan, no comparison between Placebo + MTX and Rituxan + MTX is made at week 24.

[c] For RA Study 1, weighted difference stratified by region (US, rest of the world) and Rheumatoid Factor (RF) status (positive >20 IU/mL, negative < 20 IU/mL) at baseline; For RA Study 2, weighted difference stratified by RF status at baseline and ≥ 20% improvement from baseline in both swollen joint count (SJC) and tender joint count (TJC) at week 24 (Yes/No).

Improvement was also noted for all components of ACR response following treatment with Rituxan, as shown in Table 3.

Table 3. Components of ACR Response at Week 24 in RA Study 1 (Modified Intent-to-Treat Population)

Inadequate Response to TNF Antagonists				
Parameter (median)	**Placebo + MTX (n=201)**		**Rituxan + MTX (n=298)**	
	Baseline	**Week 24**	**Baseline**	**Week 24**

Tender Joint Count	31.0	27.0	33.0	13.0
Swollen Joint Count	20.0	19.0	21.0	9.5
Physician Global Assessment[a]	71.0	69.0	71.0	36.0
Patient Global Assessment[a]	73.0	68.0	71.0	41.0
Pain[a]	68.0	68.0	67.0	38.5
Disability Index (HAQ)[b]	2.0	1.9	1.9	1.5
CRP (mg/dL)	2.4	2.5	2.6	0.9

ACR: American College of Rheumatology; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; MTX: methotrexate; RA: rheumatoid arthritis; TNF: tumor necrosing factor.
[a] Visual Analogue Scale: 0 = best, 100 = worst.
[b] Disability Index of the Health Assessment Questionnaire: 0 = best, 3 = worst.

Although both treatment groups received a brief course of intravenous and oral glucocorticoids resulting in similar benefits at week 4, higher ACR 20 responses were observed for the Rituxan group by week 8. A similar proportion of patients achieved these responses through week 24 after a single course of treatment (2 infusions) with Rituxan. Similar patterns were demonstrated for ACR 50 and 70 responses.

Radiographic Response
In RA Study 1, structural joint damage was assessed radiographically and expressed as changes in Genant-modified Total Sharp Score (TSS) and its components, the erosion score (ES) and the joint space narrowing (JSN) score. Rituxan + MTX slowed the progression of structural damage compared to placebo + MTX after 1 year as shown in Table 4.

Table 4. Mean Radiographic Change from Baseline to 104 Weeks in RA Study 1

Inadequate Response to TNF Antagonists				
Parameter	**Rituxan 2 x 1000 mg + MTX[b]**	**Placebo + MTX[c]**	**Treatment Difference (Placebo-Rituxan)**	**95% CI**
Change During First Year				
TSS	0.66	1.77	1.11	(0.47, 1.75)
ES	0.44	1.19	0.75	(0.32, 1.19)
JSN Score	0.22	0.58	0.36	(0.10, 0.62)
Change During Second Year[a]				
TSS	0.48	1.04	-	-
ES	0.28	0.62	-	-
JSN Score	0.20	0.42	-	-

CI: confidence interval; ES: erosion score; JSN: joint space narrowing score; MTX: methotrexate; RA: rheumatoid arthritis; TNF: tumor necrosing factor; TSS: Genant-modified Total Share Score.
[a] Based on radiographic scoring following 104 weeks of observation.
[b] Patients received up to 2 years of treatment with Rituxan + MTX.
[c] Patients receiving Placebo + MTX. Patients receiving Placebo + MTX could have received retreatment with Rituxan + MTX from week 16 onward.

In RA Study 1 and its open-label extension, 70% of patients initially randomized to Rituxan + MTX and 72% of patients initially randomized to placebo + MTX were evaluated radiographically at Year 2. As shown in Table 4, progression of structural damage in Rituxan + MTX patients was further reduced in the second year of treatment.

Following 2 years of treatment with Rituxan + MTX, 57% of patients had no progression of structural damage. During the first year, 60% of Rituxan + MTX treated patients had no progression, defined as a change in TSS of zero or less compared to baseline, compared to 46% of placebo + MTX treated patients. In their second year of treatment with Rituxan + MTX, more patients had no progression than in the first year (68% vs. 60%), and 87% of the Rituxan + MTX treated patients who had no progression in the first year also had no progression in the second year.

Lesser Efficacy of 500 vs. 1000 mg Treatment Courses for Radiographic Outcomes
RA Study 3 (NCT00299104) is a randomized, double-blind, placebo-controlled study which evaluated the effect of placebo + MTX compared to Rituxan 2 x 500 mg + MTX and Rituxan 2 x 1000 mg + MTX treatment courses in MTX-naïve RA patients with moderately to severely active disease. Patients received a first course of two infusions of rituximab or placebo on Days 1 and 15. MTX was initiated at 7.5 mg/week and escalated up to 20 mg/week by week 8 in all three treatment arms. After a minimum of 24 weeks, patients with ongoing disease activity were eligible to receive re-treatment with additional courses of their assigned treatment. After one year of treatment, the proportion of patients achieving ACR 20/50/70 responses were similar in both Rituxan dose groups and were higher than in the placebo group. However, with respect to radiographic scores, only the Rituxan 1000 mg treatment group demonstrated a statistically significant reduction in TSS: a change of 0.36 units compared to 1.08 units for the placebo group, a 67% reduction.

Physical Function Response
RA Study 4 (NCT00299130) is a randomized, double-blind, placebo-controlled study in adult RA patients with moderately to severely active disease with inadequate response to MTX. Patients were randomized to receive an initial course of Rituxan 500 mg, Rituxan 1000 mg, or placebo in addition to background MTX.

Physical function was assessed at weeks 24 and 48 using the Health Assessment Questionnaire Disability Index (HAQ-DI). From baseline to week 24, a greater proportion of Rituxan-treated patients had an improvement in HAQ-DI of at least 0.22 (a minimal clinically important difference) and a greater mean HAQ-DI improvement compared to placebo, as shown in Table 5. HAQ-DI results for the Rituxan 500 mg treatment group were similar to the Rituxan 1000 mg treatment group; however radiographic responses were not assessed (see Dosing Precaution in the Radiographic Responses section above). These improvements were maintained at 48 weeks.

Table 5. Improvement from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 24 in RA Study 4

	Placebo + MTX n=172	Rituxan 2 x 1000mg + MTX n=170	Treatment Difference (Rituxan – Placebo)[b] (95% CI)
Mean Improvement from Baseline	0.19	0.42	0.23 (0.11, 0.34)
Percent of Patients with "Improved" score (Change from Baseline ≥MCID)[a]	48%	58%	11% (0%, 21%)

CI: confidence interval; MTX: methotrexate.

[a] Minimal Clinically Important Difference: MCID for HAQ = 0.22.

[b] Adjusted difference stratified by region (US, rest of the world) and rheumatoid factor (RF) status (positive ≥ 20 IU/mL, negative < 20 IU/mL) at baseline.

Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) (1-4)

Induction Treatment of Adult Patients with Active Disease (GPA/MPA Study 1)

A total of 197 patients with active, severe GPA and MPA (two forms of antineutrophil cytoplasmic antibody [ANCA]-associated vasculitides) were treated in a randomized, double-blind, active-controlled, multicenter, non-inferiority study, conducted in two phases – a 6-month remission induction phase and a 12-month remission maintenance phase. Patients were 15 years of age or older, diagnosed with GPA (75% of patients) or MPA (24% of patients) according to the Chapel Hill Consensus conference criteria (1% of the patients had unknown vasculitis type). All patients had active disease, with a Birmingham Vasculitis Activity Score for Granulomatosis with Polyangiitis (BVAS/GPA) ≥ 3, and their disease was severe, with at least one major item on the BVAS/GPA. Ninety-six (49%) of patients had new disease and 101 (51%) of patients had relapsing disease.

Patients in both arms received 1000 mg of pulse intravenous methylprednisolone per day for 1 to 3 days within 14 days prior to initial infusion. Patients were randomized in a 1:1 ratio to receive either Rituxan 375 mg/m^2 once weekly for 4 weeks or oral cyclophosphamide 2 mg/kg daily for 3 to 6 months in the remission induction phase. Patients were pre-medicated with antihistamine and acetaminophen prior to Rituxan infusion. Following intravenous corticosteroid administration, all patients received oral prednisone (1 mg/kg/day, not exceeding 80 mg/day) with pre-specified tapering. Once remission was achieved or at the end of the 6-month remission induction period, the cyclophosphamide group received azathioprine to maintain remission. The Rituxan group did not receive additional therapy to maintain remission. The main outcome measure for both GPA and MPA patients was achievement of complete remission at 6 months defined as a BVAS/GPA of 0, and off glucocorticoid therapy. The pre-specified non-inferiority margin was a treatment difference of 20%. As shown in Table

6, the study demonstrated non-inferiority of Rituxan to cyclophosphamide for complete remission at 6 months.

Table 6. Percentage of Patients with GPA/MPA Who Achieved Complete Remission at 6 months (Intent-to-Treat Population)

	Rituxan (n=99)	Cyclophosphamide (n=98)	Treatment Difference (Rituxan – Cyclophosphamide)
Rate	64%	53%	11%
95.1%[b] CI	(54%, 73%)	(43%, 63%)	(-3%, 24%)[a]

CI: confidence interval; GPA: Granulomatosis with Polyangiitis; MPA: Microscopic Polyangiitis.
[a] Non-inferiority was demonstrated because the lower bound was higher than the prespecified non-inferiority margin (-3% > -20%).
[b] The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim efficacy analysis.

Complete Remission (CR) at 12 and 18 months
In the Rituxan group, 44% of patients achieved CR at 6 and 12 months, and 38% of patients achieved CR at 6, 12, and 18 months. In patients treated with cyclophosphamide (followed by azathioprine for maintenance of CR), 38% of patients achieved CR at 6 and 12 months, and 31% of patients achieved CR at 6, 12, and 18 months.

Retreatment of Flares with Rituxan
Based upon investigator judgment, 15 patients received a second course of Rituxan therapy for treatment of relapse of disease activity which occurred between 8 and 17 months after the induction treatment course of Rituxan.

Follow up Treatment of Adult Patients with GPA/MPA who have achieved disease control with other Immunosuppressant (GPA/MPA Study 2)
A total of 115 patients (86 with GPA, 24 with MPA, and 5 with renal-limited ANCA-associated vasculitis) in disease remission were randomized to receive azathioprine (58 patients) or non-U.S.-licensed rituximab (57 patients) in this open-label, prospective, multi-center, randomized, active-controlled study. Eligible patients were 21 years and older and had either newly diagnosed (80%) or relapsing disease (20%). A majority of the patients were ANCA-positive. 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 (based on BVAS of 0), were randomized in a 1:1 ratio to receive either non-U.S.-licensed rituximab or azathioprine.

The non-U.S.-licensed rituximab was administered as two 500 mg intravenous infusions separated by two weeks (on Day 1 and Day 15) followed by a 500 mg intravenous infusion every 6 months for 18 months. Azathioprine was administered orally at a dose of 2 mg/kg/day for 12 months, then 1.5 mg/kg/day for 6 months, and finally 1 mg/kg/day for 4 months; treatment was discontinued after 22 months. Prednisone treatment was tapered and then kept at a low dose (approximately 5 mg per day) for at least 18 months after randomization. Prednisone dose

tapering and the decision to stop prednisone treatment after month 18 were left at the investigator's discretion.

Planned follow-up was until month 28 (10 or 6 months, respectively, after the last non-U.S.-licensed rituximab infusion or azathioprine dose). 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 non-U.S.-licensed 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 non-U.S.-licensed rituximab relative to azathioprine.

Treatment of Pediatric Patients (GPA/MPA Study 4)
The study design consisted of an initial 6-month remission induction phase and a minimum 12-month follow-up phase up to a maximum of 54 months (4.5 years) in pediatric patients 2 years to 17 years of age with GPA and MPA. Patients were to receive a minimum of 3 doses of intravenous methylprednisolone (30 mg/kg/day, not exceeding 1g/day) prior to the first Rituxan or non-U.S.-licensed rituximab intravenous infusion. If clinically indicated, additional daily doses (up to three), of intravenous methylprednisolone could be given. The remission induction regimen consisted of four once weekly intravenous infusions of Rituxan or non-U.S.-licensed 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 (max 60 mg/day) tapered to 0.2 mg/kg/day minimum (max 10 mg/day) by Month 6. After the remission induction phase, patients could receive subsequent Rituxan or non-U.S.-licensed rituximab intravenous infusions on or after Month 6 to maintain remission and control disease activity.

The primary objectives of this study were to evaluate safety and pharmacokinetics (PK) parameters in pediatric GPA and MPA patients (2 years to 17 years of age). The efficacy objectives of the study were exploratory and principally assessed using the Pediatric Vasculitis Activity Score (PVAS).

A total of 25 pediatric patients 6 years to 17 years of age with active GPA and MPA were treated with Rituxan or non-U.S.-licensed rituximab in a multicenter, open-label, single-arm, uncontrolled study (NCT01750697). The median age of patients in the study was 14 years and the majority of patients (20/25 [80%]) were female. A total of 19 patients (76%) had GPA and 6 patients (24%) had MPA at baseline. Eighteen patients (72%) had newly diagnosed disease upon study entry (13 patients with GPA and 5 patients with MPA) and 7 patients had relapsing disease (6 patients with GPA and 1 patient with MPA).

All 25 patients completed all four once weekly intravenous infusions for the 6-month remission induction phase. A total of 24 out of 25 patients completed at least 18 months from Day 1 (baseline).

The exploratory efficacy using the PVAS is described in Table 7.

Table 7. Percentage of Patients Who Achieved PVAS Remission by Month 6, 12 and 18 (*GPA/MPA Study 4*)

Time to Follow-Up Since Day 1			
	Month 6 n=25	**Month 12 n=25**	**Month 18 n=25**
Response Rate	56%	92%	100%
95% CI[a]	(34.9%, 76.6%)	74.0%, 99.0%)	(86.3%, 100.0%)

CI: confidence interval; GPA: Granulomatosis with Polyangiitis; MPA: Microscopic Polyangiitis; PVAS: Pediatric Vasculitis Activity Score.

*PVAS remission is defined by a PVAS of 0 and achieved glucocorticoid taper to 0.2 mg/kg/day (or 10 mg/day, whichever is lower), or a PVAS of 0 on two consecutive readings ≥4 weeks apart irrespective of glucocorticoid dose

[a] The efficacy results are exploratory and no formal statistical testing was performed for these endpoints.

Follow-Up Treatment

After the 6-month remission induction phase, patients who had not achieved remission or who had progressive disease or flare that could not be controlled by glucocorticoids alone received additional treatment for GPA and MPA that could include Rituxan or non-U.S.-licensed rituximab and/or other therapies, at the discretion of the investigator. Planned follow-up was until Month 18 (from Day 1).

Fourteen out of 25 patients (56%) received additional Rituxan or non-U.S.-licensed rituximab treatment at or post Month 6, up to Month 18. Five of these patients received four once weekly doses (375 mg/m^2) of intravenous Rituxan or non-U.S.-licensed rituximab approximately every 6 months; 5 of these patients received a single dose (375 mg/m^2) of Rituxan or non-U.S.-licensed rituximab every 6 months, and 4 of these patients received various other Rituxan or non-U.S.-licensed rituximab doses/regimens according to investigator. Of the 14 patients who received follow-up treatment between Month 6 and Month 18, 4 patients first achieved remission between Months 6 and 12 and 1 patient first achieved remission between Months 12 and 18. Nine of these 14 patients achieved PVAS remission by Month 6 but required additional follow-up treatment after Month 6.

Pemphigus Vulgaris (PV) (1-4)

PV Study 1 (NCT00784589)

Non-U.S.-licensed rituximab in combination with short-term prednisone was compared to prednisone monotherapy as first-line treatment in 90 newly diagnosed adult patients with moderate to severe pemphigus (74 Pemphigus Vulgaris [PV] and 16 Pemphigus Foliaceus [PF])

in this randomized, open-label, controlled, multicenter study (PV Study 1). Patients were between 19 and 79 years of age and had not received prior therapies for pemphigus. In the PV population, 5 (13%) patients in the group treated with non-U.S.-licensed rituximab and 3 (8%) patients in the prednisone group had moderate disease and 33 (87%) patients in the group treated with non-U.S.-licensed rituximab and 33 (92%) patients in the prednisone group had severe disease according to disease severity defined by Harman's criteria.

Patients were stratified by baseline disease severity (moderate or severe) and randomized 1:1 to receive either the non-U.S.-licensed rituximab and short-term prednisone or long-term prednisone monotherapy. Patients were pre-medicated with antihistamine, acetaminophen and methylprednisolone prior to infusion of the non-U.S.-licensed rituximab. Patients randomized to the group treated with non-U.S.-licensed rituximab received an initial intravenous infusion of 1000 mg non-U.S.-licensed rituximab on Study Day 1 in combination with a short-term regimen of 0.5 mg/kg/day oral prednisone tapered off over 3 months if they had moderate disease or 1 mg/kg/day oral prednisone tapered off over 6 months if they had severe disease. All patients received a second intravenous infusion of 1000 mg non-U.S.-licensed rituximab on Study Day 15. Maintenance infusions of 500 mg non-U.S.-licensed rituximab were administered at Months 12 and 18. Patients randomized to the prednisone monotherapy group received an initial 1 mg/kg/day oral prednisone tapered off over 12 months if they had moderate disease or 1.5 mg/kg/day oral prednisone tapered off over 18 months if they had severe disease. Patients in the group treated with non-U.S.-licensed rituximab who relapsed could receive an additional infusion of 1000 mg non-U.S.-licensed rituximab in combination with reintroduced or escalated prednisone dose. Maintenance and relapse infusions were administered no sooner than 16 weeks following the previous infusion.

The primary endpoint for the study was complete remission (complete epithelialization and absence of new and/or established lesions) at Month 24 without the use of prednisone therapy for 2 months or more (CRoff for ≥2 months). The results of the trial are presented in Table 8.

Table 8. Percentage of Pemphigus Patients in Complete Remission off Corticosteroid Therapy for Two Months of More (CRoff ≥2 months) at Month 24, PV Study 1 (Intent-to Treat Population)

	Non-U.S.-Licensed Rituximab + Short-Term Prednisone N=46	**Prednisone N=44**
Number of responders (response rate [%])	41 (89%)	15 (34%)
PV patients	34/38 (90%)	10/36 (28%)
PF patients	7/8 (88%)	5/8 (63%)

PF: pemphigus foliaceus; PV: pemphigus vulgaris; U.S. United States.

PV Study 2 (NCT02383589)

In a randomized, double-blind, double-dummy, active-comparator, multicenter study, the efficacy and safety of Rituxan compared to mycophenolate mofetil (MMF) were evaluated in

patients with moderate-to-severe PV receiving 60-120 mg/day oral prednisone or equivalent (1.0-1.5 mg/kg/day) at study entry and tapered to reach a dose of 60 or 80 mg/day by Day 1. Patients had a confirmed diagnosis of PV within the previous 24 months and evidence of moderate-to-severe disease defined as a total Pemphigus Disease Area Index (PDAI) activity score of greater than or equal to 15. The study consisted of a screening period of up to 28 days, a 52-week double-blind treatment period, and a 48-week safety follow up period.

One hundred and thirty-five patients were randomized to treatment with Rituxan 1,000 mg administered on Day 1, Day 15, Week 24 and Week 26 or oral MMF 2 g/day (starting at 1 g/day on Day 1 and titrated to achieve a goal of 2 g/day by Week 2) for 52 weeks in combination with an initial dose of 60 or 80 mg oral prednisone with the aim of tapering to 0 mg/day by Week 24. Randomization was stratified by duration of PV (within the 1 year prior to screening or greater than 1 year) and geographical region. A dual-assessor approach was used during the study for efficacy and safety evaluations to prevent potential unblinding.

One hundred and twenty-five patients (excluding exploratory data from ten telemedicine patients) were analyzed for efficacy (Modified Intent-to-Treat Population). The primary efficacy endpoint for this study was the proportion of subjects achieving sustained complete remission defined as achieving healing of lesions with no new active lesions (i.e., PDAI activity score of 0) while on 0 mg/day prednisone or equivalent, and maintaining this response for at least 16 consecutive weeks, during the 52-week treatment period. Secondary endpoints included cumulative oral corticosteroid dose and the total number of disease flares.

The results of the trial are presented in Table 9.

Table 9. Percentage of PV Patients Who Achieved Sustained Complete Remission Off Corticosteroid Therapy for 16 Weeks or More at Week 52 (Modified Intent-to-Treat Population)

	Rituxan (N=62)	**MMF (N=63)**	**Difference (95% CI)**
Number of responders (response rate [%])	25 (40.3%)	6 (9.5%)	30.80% (14.70%, 45.15%)

CI: confidence Interval; MMF: mycophenolate mofetil; PV: pemphigus vulgaris.

Glucocorticoid exposure

The median (min, max) cumulative oral prednisone dose at Week 52 was 2775 mg (450, 22180) in the Rituxan group compared to 4005 mg (900, 19920) in the MMF group. Topical corticosteroid use and pre-infusion intravenous (IV) methylprednisolone were not included in this analysis. Prior to each infusion, the Rituxan group received IV methylprednisolone 100 mg and the MMF group received IV saline solution.

Disease flare

Disease flare was defined as an appearance of 3 or more new lesions a month that do not heal spontaneously within 1 week or by the extension of established lesions in a patient who has

achieved disease control. The total number of disease flares was lower in patients treated with Rituxan compared to MMF (6 vs. 44).

NON-FDA LABELED INDICATIONS

Hepatitis C Virus-Associated Cryoglobulinemic Vasculitis

Systematic Reviews

Dammacco et al. (2013) (11) and Puéchal and Guillevin (2013) (12) published reviews of HCV-associated cryoglobulinemic vasculitis. Previous treatment recommendations, (13) recently published RCTs, (14, 15) and heterogeneous nonrandomized studies (that varied by design, HCV genotype, previous treatment, rituximab dose, concomitant therapy) (total N=377) reported response rates of approximately 80%, and led reviewers to draw the following conclusions: (11, 12)

- The choice of the most suitable treatment for a given patient should be based on the level of disease activity and the extent and severity of organ involvement.
    - For patients with mild-to-moderate disease activity, antiviral therapy was recommended as first-line treatment.
    - For patients with active disease resistant to antiviral agents, and for patients with severe (e.g., leg ulcers, glomerulonephritis, peripheral neuropathy) or life-threatening cryoglobulinemic vasculitis, the addition of rituximab (or other B-cell-depleting monoclonal antibody) may slow or halt disease progression.
    - Pegylated interferon alfa may exacerbate some clinical features of cryoglobulinemic vasculitis, such as skin ulcers and peripheral neuropathy.
    - When rituximab is added, plasmapheresis and immunosuppressive therapy also should be added.
- Optimal rituximab dosing for vasculitis has not been determined. Most patients in studies received 4 weekly infusions of 375 mg/m^2.
- One gram dosing of rituximab may precipitate cryoglobulin.
- HCV load, which does not appear to be associated with detectable adverse events on the liver or with HCV reactivation, may increase during rituximab therapy.
- Viral load and liver function tests should be monitored at regular intervals during rituximab treatment.

More recently, Covic et al. (2023) published a systematic review that continues to support the efficacy of rituximab in this setting, either alone or with antiviral therapy. (16)

Nonrandomized Studies

Visentini et al. (2015) reported on the results from a phase 2 trial (EUDRACT) addressing rituximab dosing in mixed cryoglobulinemia. (17) Fifty-two patients with HCV-associated disease, either ineligible or intolerant of antivirals, were treated with low-dose rituximab (250 mg/m^2x2). The response was evaluated at 3, 6, and 12 months and then compared with historical results from 19 published studies. A CR or PR was observed in 81% of patients by 3 months compared with 86% in 208 patients in prior studies treated with high-dose rituximab (375 mg/m^2 weekly for 4 weeks). Adverse events attributed to treatment were identified in

11.5% of patients compared with 19.9% in the high-dose studies. The investigators suggested this low-dose regimen may have similar efficacy to a high-dose regimen.

Clinical Input

Churg-Strauss Syndrome

Consensus input concerning the treatment of Churg-Strauss syndrome considers rituximab as medically necessary and supports as first-line use (induction therapy) for severe disease.

Other

Other off-label uses of rituximab (Rituxan®) and associated biosimilars may be considered medically necessary for the specific indications listed in coverage, as those indications have been recognized as having an acceptable level of evidence in a prescription drug reference compendium for treatment of the indication for which the drug is prescribed.

Practice Guidelines and Position Statements

American Academy of Neurology

In 2018, the American Academy of Neurology (AAN) updated its guidelines on disease-modifying therapies for adults with multiple sclerosis (MS); these guidelines were reaffirmed in 2021. (18) For patients with relapse-remitting MS, rituximab was judged to be likely more effective than placebo regarding the decreased risk of relapse at 1 year, as well as the decreased volume of T2 lesions from baseline to week 36, with a moderate confidence in the evidence (1 class II study). However, the evidence on the efficacy of rituximab in decreased annualized relapse rates at 1 year compared with placebo was insufficient (very low confidence in the evidence). The evidence is also insufficient regarding adverse event-related withdrawal and infection-associated serious adverse events following rituximab versus placebo (very low confidence in the evidence). For patients with progressive MS, rituximab was not found to be more effective than placebo in reducing the risk of disease progression over 2 years (low confidence in the evidence). Overall, the AAN recommended that clinicians counsel patients considering rituximab or other immunosuppressive agents regarding treatment risks (level B recommendation).

American College of Rheumatology (ACR)

In 2012, the American College of Rheumatology published evidence-based consensus guidelines on the treatment of lupus nephritis. (19) A task force panel voted that, in some cases, rituximab can be used in patients whose nephritis fails to improve or worsens after 6 months of 1 induction therapy, or after the patient has failed both cyclophosphamide and mycophenolate mofetil treatments (level C evidence, based on consensus, expert opinion, or case series). The guidelines are currently being updated and anticipated in the first half of 2025. (20)

In 2020, the ACR published guidelines for the management of pulmonary disease in patients with Sjögren syndrome. (21) The following recommendations were made regarding the use of rituximab in this setting:

- "If initial treatment with MMF [mycophenolate mofetil] or azathioprine is insufficient or not tolerated in Sjögren's patients with interstitial lung disease (ILD) who are symptomatic and

in whom pulmonary function tests (PFTs) or high-resolution CT [computed tomography] (HRCT) demonstrated moderate-severe impairment, subsequent second-line maintenance drugs may include rituximab and calcineurin inhibitors, cyclosporine, or tacrolimus." (Strength of Evidence: low; Strength of Recommendation: weak)
- "In a Sjögren's patient with ILD who has acute or subacute hypoxic respiratory failure requiring hospitalization, despite initial therapies, rituximab or cyclophosphamide should be considered in addition to high-dose corticosteroids." (Strength of Evidence: low; Strength of Recommendation: moderate)

The 2021 ACR/Vasculitis Foundation guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis recommends rituximab in the setting of severe granulomatosis with polyangiitis and microscopic polyangiitis, but not specifically eosinophilic granulomatosis with polyangiitis. (22)

International Society on Thrombosis and Haemostasis

In 2020, the International Society on Thrombosis and Haemostasis (ISTH) published guidelines for the treatment of thrombotic thrombocytopenic purpura (TTP). (23) The following recommendations were made regarding the use of rituximab in immune-mediated TTP (iTTP):
- "For patients with iTTP experiencing their first acute event, the panel suggests the addition of rituximab thrombotic thrombocytopenic purpurato corticosteroids and therapeutic plasma exchange (TPE) over corticosteroids and TPE alone. (A conditional recommendation in the context of very low certainty evidence.)"
- "For patients with iTTP experiencing a relapse, the panel suggests the addition of rituximab to corticosteroids and TPE over corticosteroids and TPE alone. (A conditional recommendation in the context of very low certainty evidence.)"
- "For patients with iTTP who are in remission, but still have low plasma ADAMTS13 activity with no clinical signs/symptoms, the panel suggests the use of rituximab over nonuse of rituximab for prophylaxis. (A conditional recommendation in the context of very low certainty evidence.)"

Kidney Disease and Improving Global Outcomes

The Kidney Disease and Improving Global Outcomes (KDIGO) guideline for the management of glomerular diseases was published in October 2021. (24) The guideline made the following relevant recommendations for glomerular diseases:

Membranous nephropathy
- "For patients with MN [membranous nephropathy] and at least one risk factor for disease progression, we recommend using rituximab or cyclophosphamide and alternate month glucocorticoids for 6 months, or CNI [calcineurin inhibitor]-based therapy for ≥6 months, with the choice of treatment depending on the risk estimate."

Minimal change disease
- "We recommend cyclophosphamide, rituximab, CNIs, or mycophenolic acid analogs (MPAA) for the treatment of frequently relapsing/steroid-dependent MCD [minimal change disease], rather than prednisone alone or no treatment."

A KDIGO guideline for the management of lupus nephritis was published in January 2024. (25) The guideline made the following practice point: "Rituximab may be considered for patients with persistent disease activity or inadequate response to initial standard-of-care therapy." In this setting, the treatment algorithm recommended adding rituximab to other biologic therapies.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 10.

Table 10. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Warm autoimmune hemolytic anemia			
NCT01181154[a]	Rituximab in Adult's Warm Auto-Immune Hemolytic Anemia: a Phase III, Double- blind, Randomised Placebo-controlled Trial	32	Jan. 2016 (completed; unpublished)
Churg-Strauss syndrome			
NCT02807103	Evaluation of Rituximab-based Regimen Compared to Conventional Therapeutic Strategy For Remission Induction in Patients With Newly-Diagnosed or Relapsing Eosinophilic Granulomatosis With Polyangiitis. Prospective, Randomized, Controlled, Double-blind Study	107	Oct 2020 (completed; unpublished)
NCT03164473	MAINtenance of Remission With RITuximab Versus Azathioprine for Patients With Newly-diagnosed or Relapsing Eosinophilic Granulomatosis With Polyangiitis. A Prospective, Randomized, Controlled, Double-blind Study: the MAINRITSEG Trial	98	Oct 2024 (active)
Systemic sclerosis			
NCT01748084	Evaluation of Rituximab in Systemic Sclerosis Associated Polyarthritis (RECOVER)	22	Apr. 2016 (completed; unpublished)
Myasthenia gravis			
NCT06342544	Immediate Corticosteroid Therapy and Rituximab to Prevent Generalization in Ocular Myasthenia: a PROBE Multicenter Open-label Randomized Controlled Trial. (IMCOMG)	128	Jun 2029

NCT05332587	Efficacy and Safety of Low-dose Rituximab in the Treatment of Refractory Myasthenia Gravis	50	Jul 2022 (completed; unpublished)
Human leukocyte antigen sensitization pretransplant			
NCT01095172[a]	A Randomized Trial of Rituximab in Induction Therapy for Living Donor Renal Transplantation	100	Oct. 2022 (active)
Lupus Nephritis			
NCT05207358	Minimizing Glucocorticoid Administration in Patients With Proliferative Lupus Nephritis During the Induction of Remission Period-EUROLUPUS vs. RITUXILUP Regimen: A Randomized Study	30	Dec 2028
Idiopathic membranous nephropathy			
NCT05514015	Clinical Study of Rituximab or Cyclophosphamide Combined With Steroids int eh Treatment of Idiopathic Membranous Nephropathy	72	Dec 2026
NCT05532111	Efficacy and Safety of Rituximab Combined With Tacrolimus in the Treatment of Intermediate-to-high Risk Primary Membranous Nephropathy: A Randomized Clinical Trial	60	Sept 2024

NCT: national clinical trial.
[a] Industry sponsored or co-sponsored.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J3490, J9312, Q5115, Q5119, Q5123

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Labels:

1. U.S. Food and Drug Administration, Drugs @ FDA. Highlights of Prescribing Information: Rituxan® (12/2021). Available at: <https://www.accessdata.fda.gov> (accessed September 19, 2025).
2. U.S. Food and Drug Administration, Drugs @ FDA. Highlights of Prescribing Information: rituximab-abbs (6/2025). Available at: <https://www.accessdata.fda.gov> (accessed September 19, 2025).
3. U.S. Food and Drug Administration, Drugs @ FDA. Highlights of Prescribing Information: rituximab-pvvr (6/2025). Available at: <https://www.accessdata.fda.gov> (accessed September 19, 2025).
4. U.S. Food and Drug Administration, Drugs @ FDA. Highlights of Prescribing Information: rituximab-arrx (6/2025). Available at: <https://www.accessdata.fda.gov> (accessed September 19, 2025).

Other:

5. Thaler KJ, Gartlehner G, Kien C, et al. Drug Class Review: Targeted Immune Modulators: Final Update 3 Report. Portland OR: Oregon Health & Science University; 2012.
6. Rituximab. In: Merative™ Micromedex® DRUGDEX® (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: <https://www.micromedexsolutions.com> (accessed September 19, 2025).
7. Rituxan® Approval History. Available at: <https://www.drugs.com> (accessed September 25, 2025).
8. Rituximab-abbs (Truxima®) Approval History. Available at: <https://www.drugs.com> (accessed September 25, 2025).
9. Rituximab-pvvr (Ruxience®) Approval History. Available at: <https://www.drugs.com> (accessed September 25, 2025).
10. Rituximab-arrx (Riabni®) Approval History. Available at: <https://www.drugs.com> (accessed September 25, 2025).
11. Dammacco F, Sansonno D. Therapy for hepatitis C virus-related cryoglobulinemic vasculitis. N Engl J Med. Sep 12 2013; 369(11):1035-1045. PMID 24024840
12. Puéchal X, Guillevin L. Therapeutic immunomodulation in systemic vasculitis: taking stock. Joint Bone Spine. Jul 2013; 80(4):374-379. PMID 23237994
13. Pietrogrande M, De Vita S, Zignego AL, et al. Recommendations for the management of mixed cryoglobulinemia syndrome in hepatitis C virus-infected patients. Autoimmun Rev. Jun 2011; 10(8):444-454. PMID 21303705
14. Sneller MC, Hu Z, Langford CA. A randomized controlled trial of rituximab following failure of antiviral therapy for hepatitis C virus-associated cryoglobulinemic vasculitis. Arthritis Rheum. Mar 2012; 64(3):835-842. PMID 22147444
15. De Vita S, Quartuccio L, Isola M, et al. A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. Arthritis Rheum. Mar 2012; 64(3):843-853. PMID 22147661
16. Covic A, Caruntu ID, Burlacu A, et al. Therapeutic Potential of Rituximab in Managing Hepatitis C-Associated Cryoglobulinemic Vasculitis: A Systematic Review. J Clin Med. Oct 27 2023; 12(21):6806. PMID 37959271

17. Visentini M, Tinelli C, Colantuono S, et al. Efficacy of low-dose rituximab for the treatment of mixed cryoglobulinemia vasculitis: Phase II clinical trial and systematic review. Autoimmun Rev. Oct 2015; 14(10):889-896. PMID 26031898
18. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. Apr 24 2018; 90(17):777-788. PMID 29686116
19. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken). Jun 2012; 64(6):797-808. PMID 22556106
20. Lupus guideline. American College of Rheumatology. nd. Available at: <https://rheumatology.org> (accessed August 28, 2024).
21. Lee AS, Scofield RH, Hammitt KM, et al. Consensus Guidelines for Evaluation and Management of Pulmonary Disease in Sjögren's. Chest. Feb 2021; 159(2):683-698. PMID 33075377
22. Chung SA, Langford CA, Maz M, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. Arthritis Rheumatol. Aug 2021; 73(8):1366-1383. PMID 34235894
23. Zheng XL, Vesely SK, Cataland SR, et al. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. J Thromb Haemost. Oct 2020; 18(10):2496-2502. PMID 32914526
24. Rovin BH, Adler SG, Barratt J, et al. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. Oct 2021; 100(4S):S1-S276. PMID 34556256
25. Rovin BH, Ayoub IM, Chan TM, et al. KDIGO 2024 Clinical Practice Guideline for the management of LUPUS NEPHRITIS. Kidney Int. Jan 2024; 105(1S):S1-S69. PMID 38182286

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
01/01/2026	Document updated. The following changes were made to Coverage: 1) Significantly revised coverage statements with the removal of multiple

	indications for use; 2) Separated coverage statements into U.S. Food and Drug Administration (FDA) labeled and non-FDA labeled indications; 3) Removed conditional statement on rheumatoid arthritis retreatment and associated NOTE 2; 4) Removed conditional statement on concurrent use of other biologic treatments for neuromyelitis optica spectrum disorder. Added references 11-17 and 23-25, others updated.
02/01/2025	Document updated. The following change was made to Coverage: Added language regarding drug shortages/recalls to "Initial Therapy" criteria. No new references added.
01/01/2025	Document updated. The following changes were made to Coverage: Added information on preferred and non-preferred products. No new references added.
09/01/2024	Document updated with literature review. The following changes were made to coverage:1) Added 'severe' to Opsoclonus myoclonus ataxia syndrome (OMAS) conditional coverage statement; 2) Added 'if no contraindication or intolerance to methotrexate exists' to Rheumatoid arthritis conditional coverage statement and 3) Reorganized label and off-label indications into one alphabetized listing. References 1, and 13-15 added; others updated.
03/15/2023	Document updated. The following changes were made to Coverage: Revised NOTE 1 to include reference to rituximab/hyaluronidase human (Rituxan Hycela). Removed the specific drug column from the table in Coverage. Added "and the biosimilars rituximab-abbs [Truxima®], rituximab-pvvr [Ruxience™], and rituximab-arrx [Riabni™])" to the non-oncologic off-label coverage statement.
08/01/2022	Document updated with literature review. The following change was made to Coverage: Added Riabni™ to list of products conditionally medically necessary in treatment of rheumatoid arthritis. Updated references 5 and 9.
05/01/2022	Document updated with literature review. The following change was made to Coverage: Added Ruxience™ to list of products conditionally medically necessary in treatment of rheumatoid arthritis. Added/updated the following references: 6-9.
05/01/2021	Document updated with literature review. The following changes were made to Coverage: 1) Added biosimilar Riabni, 2) Added clarification to neuromyelitis optica relating to concurrent biologic administration, and 3) Revised experimental, investigational and/or unproven statement to clarify that all uses of rituximab (Rituxan®) and rituximab biosimilars (i.e., Truxima® and Ruxience™) not specified as medically necessary are included. Reference 5 added.
07/01/2020	Document updated with literature review. Coverage revised to include biosimilars rituximab-abbs (Truxima) and rituximab-pvvr (Ruxience); added dermatomyositis and removed Waldenström's macroglobulinemia and multicentric Castleman's disease under off-label indications.

04/01/2020	Partial update. Coverage revised to remove all oncologic indications. Added Notes to Coverage and Description to refer to RX502.061 Oncology Medications for oncologic indications of Rituximab (Rituxan) and biosimilars. Description and rationale revised to remove all oncologic information. References revised and renumbered; removed references 196-235, 248-254.
06/15/2018	Partial Update. The following indication added to the off-label medically necessary indications: opsoclonus myoclonus ataxia syndrome (OMAS) that is refractory to steroids, chemotherapy and intravenous immunoglobulins (IVIG).
03/15/2018	Document updated with literature review. Removal of wording "in treatment-refractory patients" for pemphigoid diseases. Medically necessary statement added for subcutaneous rituximab (Rituxan Hycela, rituximab and hyaluronidase human) in selected patients with follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and chronic lymphocytic leukemia (CLL) who have received at least one full dose of intravenous rituximab. In addition, "as maintenance therapy after treatment-induced remission" added to coverage indication: "Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP) or as maintenance therapy after treatment-induced remission." References and Rationale significantly revised.
04/15/2017	Document updated with literature review. The following were added to non-FDA-labeled indications listed in the coverage section: 1) idiopathic membranous nephropathy, and 2) myasthenia gravis, refractory.
03/15/2016	Document updated with literature review. The following was added to the non-FDA-labeled indications: 1) Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis): as first-line treatment in combination with corticosteroids for patients with severe (organ threatening) disease or add-on therapy for treatment-refractory disease; 2) Factor inhibitors in patients with hemophilia who are refractory to conventional first-line treatments (e.g., immune tolerance induction, corticosteroids with or without cyclophosphamide), preferably as add-on therapy; 3) Add-on therapy for patients with hepatitis C virus (HCV)–associated cryoglobulinemic vasculitis who have active disease resistant to anti-viral drugs; or severe or life-threatening cryoglobulinemic vasculitis; 4) The following pemphigoid diseases in treatment-refractory patients: bullous pemphigoid, mucous membrane pemphigoid, including ocular cicatricial pemphigoid, and epidermolysis bullosa acquisita; 5) Add-on therapy for lupus nephritis refractory to at least standard first-line treatment regimens; and 6) Systemic sclerosis (scleroderma) in patients refractory to first-line treatment.
02/01/2015	Reviewed. No changes.
07/15/2013	Document updated with literature review. The following FDA non-labeled indications were added as considered medically necessary 1) B-cell or other

	Lymphoid malignancies that express CD-20 antigen (including but not limited to chronic lymphoid leukemia (CLL), in combination with fludarabine for first-line treatment, chronic lymphoid leukemia (CLL), relapsed or refractory, AIDS-related B-cell lymphoma, mantle cell lymphoma (MCL), Burkett lymphoma, marginal Zone B-Cell lymphoma, Hairy Cell Leukemia, relapsed or refractory);2) Acute lymphocytic leukemia (ALL) (3) Minimal change disease (MCD) [also known as lipoid nephrosis or nil disease] refractory, steroid-dependent or steroid-resistant; (4) Sensitized kidney transplant recipients for inhibition of antibody production; (5) Neuromyelitis optica; (6) Polymyositis; severe, refractory; (7) Rheumatoid arthritis, in combination with methotrexate, in patients with an inadequate response to methotrexate; (8) Systemic lupus erythematosus, refractory to immunosuppressive therapy; (9) Primary Sjögren's syndrome, (10) Pemphigus vulgaris was modified to include other autoimmune blistering skin diseases. The coverage for FDA labeled indications for treatment of rheumatoid arthritis and other chronic inflammatory conditions is unchanged but was moved to this Medical Policy from RX501.051. Policy title changed from Rituxan (Rituximab) for Treatment of Cancer and Hematologic Conditions.
05/01/2011	Medical document updated with new FDA approved indication. A medically necessary statement was added for Rituxan as a single agent maintenance therapy for the indication of non-Hodgkin's lymphoma for patients achieving a complete or partial response to Rituxan in combination with chemotherapy.
07/15/2010	Medical document updated with literature review. Added the following changes: 1) New FDA approved indication for Rituxan: Chronic Lymphocytic Leukemia (CLL) in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL. 2) Updated rationale on experimental, investigational and unproven coverage position pertaining to maintenance therapy.
02/01/2010	New medical document with literature review. Coverage position is conditional addressing FDA labeled and off-label indications.

Appendix

The Appendix is not applicable to plans regulated by the Illinois Department of Insurance or Medicare or Medicaid plans.

Continuation Therapy:
Continuation of therapy with non-preferred agents **is considered medically necessary** for all members (including new members):

- Who are currently receiving the requested medication for an indication listed below, AND

- Who are experiencing benefit from therapy as evidenced by disease stability or disease improvement; AND
- When dosing is in accordance with an authoritative source.

Initial Therapy:
Coverage for non-preferred agents will be provided contingent to the criteria in this section. For individuals initiating therapy, the following criteria would apply prior to non-preferred agent use:

- Individual has tried and failed, is intolerant to, or has a clinical contraindication to the preferred agent; AND
- Physician attests that in their clinical opinion, the same intolerance, contraindications, lack of clinical efficacy, or adverse event would not be expected to occur with non-preferred agents;

OR

- The preferred drugs are experiencing documented drug shortages or recalls from a wholesaler, manufacturer, the ASHP (American Hospital of Health-System Pharmacist) Drug Shortage web page or the US Food and Drug Administration.

State specific drug criteria my apply.

Preferred Drugs	Non-Preferred Drugs
Ruxience Riabni Truxima	Rituxan Rituxan Hycela