Policy Number	**RX502.030**
Policy Effective Date	**02/01/2025**
Policy End Date	**12/31/2025**

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 peer-reviewed scientific literature. 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 acceptable standards of medical practice. 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.**

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).

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	Rituxan Rituxan Hycela Truxima

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

- Autoimmune hemolytic anemia (AIHA);
- Autoimmune blistering skin diseases, severe;
- 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;
- Evans syndrome, refractory to immunosuppressive therapy;
- 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;
- Graft-versus-host disease, chronic, steroid-refractory;
- 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.
- Idiopathic membranous nephropathy;
- Lupus nephritis, as add-on therapy for patients who are refractory to at least standard first-line treatment regimens;
- Minimal change disease (MCD) [also known as lipoid nephrosis or nil disease], refractory, steroid-dependent or steroid-resistant;
- Myasthenia gravis, refractory;
- Neuromyelitis optica:
  - Will not receive rituximab concurrently with other biologics used to treat Neuromyelitis Optica Spectrum Disorder (NMOSD) (e.g., eculizumab, inebilizumab-cdon, satralizumab);
- Opsoclonus myoclonus ataxia syndrome (OMAS), severe, refractory;
- Pemphigoid diseases:
  - Bullous pemphigoid,
  - Mucous membrane pemphigoid, including ocular cicatricial pemphigoid, and epidermolysis bullosa acquisita;
- Pemphigus vulgaris, moderate to severe in adult patients;
- Polymyositis or dermatomyositis; severe, refractory;
- Primary Sjögren's syndrome;
- Renal transplant recipients, sensitized for inhibition of antibody production;
- Relapsing-remitting multiple sclerosis;
- Rheumatoid arthritis, for moderately to severely active disease, in combination with methotrexate (if no contraindication or intolerance to methotrexate exists) in patients who have had an inadequate response to methotrexate **OR** a tumor necrosing factor (TNF) antagonist.

- Re-treatment in adult patients with moderately to severely-active RA may be considered medically necessary when the patient meets ALL the following criteria as documented in the medical record:
    - Patient has received an adequate response (*NOTE 2); AND
    - An interval of no less than 16 weeks has passed since the previous dose.
- Systemic lupus erythematosus, refractory to immunosuppressive therapy;
- Systemic sclerosis (scleroderma) in patients' refractory to first-line treatment;
- Thrombocytopenic purpura, (immune, thrombotic [TTP] or idiopathic [ITP]).

***NOTE 2:** Response is defined by criteria such as American College of Rheumatology (ACR) 20 or 1.2-point improvement on the Disease Activity Score on 28 joints (DAS28) OR symptomatic improvement as evidenced by a decrease in joint pain, joint swelling, etc.

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

None.

Description

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. (1) 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.

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. (1) Rituximab reduces the number of B cells in the peripheral blood and in lymphoid tissues, thereby interrupting pathogenic processes of autoimmune diseases.

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. (2-6)

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 medical policy was originally created in 2010 and is based on the studies provided to the U.S. Food and Drug Administration for labeled indications as well as research of the compendia for non-labeled indications through April 2024.

Rheumatoid Arthritis (7-9)

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 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%)

RA: rheumatoid arthritis.
ACR: American College of Rheumatology.
TNF: tumor necrosing factor.
MTX: methotrexate.
CI: confidence interval.
[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

RA: rheumatoid arthritis.
ACR: American College of Rheumatology.
TNF: tumor necrosing factor.
MTX: methotrexate.
CRP: C-reactive protein.
HAQ: Health Assessment Questionnaire.
[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 1000mg + 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	-	-

RA: rheumatoid arthritis.
ACR: American College of Rheumatology.
TNF: tumor necrosing factor.
MTX: methotrexate.
CI: confidence interval.
TSS: Genant-modified Total Share Score.
ES: erosion score.
JSN: joint space narrowing 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%)

RA: rheumatoid arthritis.
MTX: methotrexate.
CI: confidence interval.
[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) (7-10)

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]

GPA: Granulomatosis with Polyangiitis.
MPA: Microscopic Polyangiitis.
CI: confidence interval.
[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%)

PVAS: Pediatric Vasculitis Activity Score.
GPA: Granulomatosis with Polyangiitis.
MPA: Microscopic Polyangiitis.
CI: confidence interval.
*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 αThe 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) (7)

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%)

PV: pemphigus vulgaris.
PF: pemphigus foliaceus.

Practice Guidelines and Position Statements

American College of Rheumatology (ACR)

In 2012, the American College of Rheumatology published evidence-based consensus guidelines on the treatment of lupus nephritis. (12) 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. (13)

In 2020, the ACR published guidelines for the management of pulmonary disease in patients with Sjögren syndrome. (14) 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. (15)

Neuromyelitis Optica Study Group

In 2014, the Neuromyelitis Optica Study Group published evidence-based consensus recommendations on the diagnosis and treatment of neuromyelitis optica. (11) Rituximab was recommended as first-line treatment, along with azathioprine, and as second-line treatment after azathioprine failure.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 9.

Table 9. Summary of Key Trials

NCT No.	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)
ANCA-associated vasculitis			
NCT02433522[a]	Extended Follow Up of the MAINRITSAN 2 Study. Comparison Between a Long Term and a Conventional Maintenance Treatment With Rituximab: a Placebo-Controlled Randomized Trial	97	Sept. 2018 (completed; unpublished)
NCT02198248	Low-dose Glucocorticoids Plus Rituximab Versus High-dose Glucocorticoids Plus Rituximab for Remission Induction in ANCA-associated Vasculitis; a Multicentre, Open Label, Randomised Control Trial	140	Jun. 2021 (unknown; unpublished)
Acquired hemophilia			
NCT01808911	Outcome of Acquired Hemophilia With Steroid Combined With Cyclophosphamide Versus Steroid Combined With Rituximab (CREHA Study)	164	Jun. 2020 (unknown; unpublished)
Immune thrombocytopenia			
NCT03304288	The Combination of Low-dose Rituximab and All-trans Retinoic Acid as the Treatment of Steroid-resistant/Relapse Immune Thrombocytopenia: A Multicenter, Randomized, Open-label Trial	168	Feb. 2021 (unknown; 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	Jul. 2024 (active)
Systemic sclerosis			
NCT01748084	Evaluation of Rituximab in Systemic Sclerosis Associated Polyarthritis (RECOVER)	22	Apr. 2016 (completed; unpublished)
Myasthenia gravis			
NCT05332587	Efficacy and Safety of Low-dose Rituximab in the Treatment of Refractory Myasthenia Gravis	50	Jul 2022 (unknown; unpublished)
Idiopathic membranous nephropathy			
NCT03018535	A Randomized Controlled Trial of Rituximab Versus Steroids and Cyclophosphamide in the Treatment of Idiopathic Membranous Nephropathy (RI CYCLO)	76	Dec. 2019 (unknown; unpublished)
NCT01508468	Prospective Randomized Multicentric Open Label Study to Evaluate Rituximab Treatment for Idiopathic Membranous Nephropathy (IMN)	80	Sept. 2016 (completed; unpublished)
NCT01955187	European Multicenter and Open-Label Controlled Randomized Trial to Evaluate the Efficacy of Sequential Treatment With Tacrolimus-Rituximab Versus Steroids Plus Cyclophosphamide in Patients With Primary Membranous Nephropathy (The STARMEN Study)	86	June 2019 (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)
NCT05514015	Clinical Study of Rituximab or Cyclophosphamide Combined With Steroids int eh Treatment of Idiopathic Membranous Nephropathy	72	Aug 2025 (active)
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 (active)

ANCA: antineutrophil cytoplasmic antibody.
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

1. 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.
2. Rituximab. In: Merative™ Micromedex® DRUGDEX® (electronic version). Merative, Ann Arbor, Michigan, USA. Available at: <https://www.micromedexsolutions.com> (accessed January 23, 2024).
3. Rituxan Approval History. Available at: <https://www.drugs.com> (accessed January 23, 2024).
4. Rituximab-abbs (Truxima) Approval History. Available at: <https://www.drugs.com> (accessed January 23, 2024).

5. Rituximab-pvvr (Ruxience) Approval History. Available at: <https://www.drugs.com> (accessed January 23, 2024).
6. Rituximab-arrx (Riabni) Approval History. Available at: <https://www.drugs.com> (accessed January 23, 2024).
7. U.S. Food and Drug Administration, Drugs @ FDA. Highlights of Prescribing Information: Rituxan (revised December 2021). Available at: <https://www.accessdata.fda.gov> (accessed January 23, 2024).
8. U.S. Food and Drug Administration, Drugs @ FDA. Highlights of Prescribing Information: Rituximab-abbs (revised February 2022). Available at: <https://www.accessdata.fda.gov> (accessed January 23, 2024).
9. U.S. Food and Drug Administration, Drugs @ FDA. Highlights of Prescribing Information: Rituximab-pvvr (revised October 2023). Available at: <https://www.accessdata.fda.gov> (accessed January 23, 2024).
10. U.S. Food and Drug Administration, Drugs @ FDA. Highlights of Prescribing Information: Rituximab-arrx (revised June 2022). Available at: <https://www.accessdata.fda.gov> (accessed January 23, 2024).
11. Trebst C, Jarius S, Berthele A, et al. Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS). J Neural. Jan 2014; 261(1):1-16. PMID 24272588
12. 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
13. Lupus guideline. American College of Rheumatology. nd. Available at: <https://rheumatology.org> (accessed April 24, 2024).
14. 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
15. 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

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**
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.