LifeWise
Health Plan of Washington

# PHARMACY / MEDICAL POLICY – 5.01.556

# Rituximab: Non-oncologic and Miscellaneous Uses

BCBSA Ref. Policy: 5.01.24

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| Effective Date: | **July 1, 2025*** |
| Last Revised: | Feb. 11, 2025 |
| Replaces: | Extracted from 5.01.550 |

*This policy has been revised. Click here to view the current policy.

RELATED MEDICAL POLICIES:

| | |
|---|---|
| 2.03.502 | Monoclonal Antibodies for the Treatment of Lymphoma |
| 5.01.550 | Pharmacotherapy of Arthropathies |
| 11.01.523 | Site of Service: Infusion Drugs and Biologic Agents |

The Site of Service Medical Necessity criteria within this policy DOES NOT apply to Alaska fully-insured members; refer to the infusion drug Medical Necessity criteria only.

Site of Service *and* the infusion drug Medical Necessity criteria apply to all other plan members.

Please contact Customer Service for more information.

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**Select a hyperlink below to be directed to that section.**



∞ Clicking this icon returns you to the hyperlinks menu above.

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## Introduction

Rituximab is a drug known as a monoclonal antibody. The drugs work with your own immune system to fight certain diseases. Rituximab attaches to and kills a certain type of immune cell known as B cells. While rituximab is often used to treat certain cancers, it also can be used for other conditions. Specifically, these conditions are those in which the B cells of the immune system incorrectly attack the body's own healthy cells. These conditions include rheumatoid arthritis, lupus, and Wegener's granulomatosis. This policy discusses when Rituxan (rituximab) and the biosimilars Riabni (rituximab-arrx), Ruxience (rituximab-pvvr) and Truxima (rituximab-abbs) may be considered medically necessary.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs providers about when a service may be covered.

## Policy Coverage Criteria

**Site of Service Medical Necessity criteria does NOT apply to Alaska fully-insured members; refer to the infusion drug Medical Necessity criteria only. Please contact Customer Service for more information.**

**Note:** This policy does not apply if the member has a lymphoid cancer diagnosis such as lymphoma, leukemia, multiple myeloma, or Waldenstrom's macroglobulinemia (for these diagnoses see policy **2.03.502 Monoclonal Antibodies for the Treatment of Lymphoma**).

We will review specific intravenous (IV) and injectable drugs for medical necessity for all ages.

For those aged 13 years or older, we also will review the site of service for medical necessity. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home.

**Drugs subject to site of service review addressed in this policy are:**

- **First-line products**:
  - Ruxience (rituximab-pvvr)
  - Truxima (rituximab-abbs)
- **Second-line products**:
  - Riabni (rituximab-arrx)
  - Rituxan (rituximab)

**Click on the links below to be directed to the related medical necessity criteria:**



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| Site of Service Administration | Medical Necessity |
|---|---|
| **Medically necessary sites of service**<br>• **Physician's office**<br>• **Infusion center**<br>• **Home infusion** | **IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost effective site:**<br>• These are the preferred **medically necessary** sites of service for specified drugs. |
| **Hospital-based outpatient setting**<br>• **Outpatient hospital IV infusion department** | **IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site.** |

| Site of Service Administration | Medical Necessity |
|---|---|
| • **Hospital-based outpatient clinical level of care** | **This site is considered medically necessary for the first 90 days for the following:**<br>• The initial course of infusion of a pharmacologic or biologic agent<br>**OR**<br>• Re-initiation of an agent after 6 months or longer following discontinuation of therapy*<br><br>**Note:** *This does not include when standard dosing between infusions is 6 months or longer<br><br>**This site is considered medically necessary when there is no outpatient infusion center within 50 miles of the patient's home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions of this drug.**<br><br>**This site is considered medically necessary only when the individual has a clinical condition which puts him or her at increased risk of complications for infusions, including any ONE of the following:**<br>• Known cardiac condition (e.g., symptomatic cardiac arrhythmia) or pulmonary condition (e.g., significant respiratory disease, serious obstructive airway disease, %FVC ≤ 40%) that may increase the risk of an adverse reaction<br>• Unstable renal function which decreases the ability to respond to fluids<br>• Difficult or unstable vascular access<br>• Acute mental status changes or cognitive conditions that impact the safety of infusion therapy<br>• A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug |

| Site of Service Administration | Medical Necessity |
|---|---|
| | **This site is considered medically necessary when the individual has cytokine release syndrome (CRS) and all the following are met:**<br>• CRS is grade 3 or 4 as evidenced by ALL the following:<br>  ○ Temperature ≥ 38 °C<br>  ○ Hypotension that requires one or more vasopressors<br>  ○ Hypoxia that requires oxygen through a high-flow nasal cannula, face mask, non-rebreather mask, or Venturi mask OR positive pressure (continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, or mechanical ventilation)<br>**AND**<br>• The individual will be admitted into an inpatient setting as soon as possible |
| **Hospital-based outpatient setting**<br>• **Outpatient hospital IV infusion department**<br>• **Hospital-based outpatient clinical level of care** | **These sites are considered not medically necessary for infusion and injectable therapy services of various medical and biologic agents when the site-of-service criteria in this policy are not met.** |

| Condition | Medical Necessity |
|---|---|
| **Ruxience and Truxima are subject to review for site of service administration.** | |
| **Arthropathies** | |
| **Rheumatoid arthritis (RA)**<br>• **See also: Related Policy 5.01.550 Pharmacotherapy of Arthropathies**<br>• **Related Policy 5.01.647 Medical Necessity Criteria for Custom Incentive and Open Formularies** | **Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary when:**<br>• Treating moderately to severely active rheumatoid arthritis (e.g., ≥8 swollen and ≥8 tender joints)<br>**AND**<br>• Is administered in combination with methotrexate<br>**AND**<br>• Is used as a **second-line** therapy when either:<br>  ○ The individual has tried and failed any one of the first line therapies listed below: |

| Condition | Medical Necessity |
|---|---|
| **Ruxience and Truxima are subject to review for site of service administration.** | |
| | ▪ A preferred adalimumab product*: Cyltezo (adalimumab-adbm), Simlandi (adalimumab-ryvk), adalimumab-adaz (Hyrimoz unbranded), adalimumab-adbm (Cyltezo unbranded), or adalimumab-ryvk (Simlandi unbranded)<br>▪ Enbrel (etanercept)<br>▪ Remicade (infliximab)<br>▪ Actemra (tocilizumab)<br>▪ Xeljanz (tofacitinib) / Xeljanz XR (tofacitinib extended release)<br>▪ Rinvoq (upadacitinib)<br>**OR**<br>○ The individual has had an inadequate response to methotrexate or other conventional synthetic disease-modifying anti-rheumatic drug (DMARD)<br>**AND**<br>○ Is not a suitable candidate for treatment with TNF inhibitors (e.g., due to a recent [i.e., within 5 years] history of lymphoma or other malignancy; latent tuberculosis, and contraindication to chemoprophylaxis; or previous demyelinating disease<br><br>***Note:** This list of preferred adalimumab products does not apply to one Open formulary (Formulary ID: 6062; Rx Plan F1) and one Incentive formulary (Formulary ID: 6064; Rx Plan G3). More details can be found in policy **5.01.647 Medical Necessity Criteria for Custom Incentive and Open Formularies**. Please check the member Plan booklet or member ID card to determine whether this list of preferred adalimumab products applies. |
| **Miscellaneous Autoimmune Diseases** | |
| **Antineutrophil cytoplasmic antibody – associated (ANCA) vasculitides:**<br>• **Wegener's granulomatosis (granulomatosis with polyangiitis)** | **Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of granulomatosis with polyangitis and microscopic polyangitis when:**<br>• Initial therapy with azathioprine, methotrexate and/or mycophenolate has been tried and failed or is contraindicated. |

| Condition | Medical Necessity |
|---|---|
| **Ruxience and Truxima are subject to review for site of service administration.** | |
| • **Microscopic polyangiitis** | **AND**<br>• Medication is used in combination with glucocorticoids. |
| **Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)** | **Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) when:**<br>• Used as first-line treatment in combination with glucocorticoids for individuals with severe (organ-threatening) disease<br>**OR**<br>• Medication is used as add-on therapy for treatment-refractory disease |
| **Cryoglobulinemic vasculitis associated with hepatitis-C virus (HCV)** | **Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of cryoglobulinemic vasculitis associated with hepatitis-C virus when:**<br>• Used as add-on therapy for individuals who have:<br>o Active disease resistant to anti-viral drugs<br>**OR**<br>o Severe or life-threatening cryoglobulinemic vasculitis |
| **Idiopathic membranous nephropathy** | **Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of idiopathic membranous nephropathy when:**<br>• The individuals have failed prior treatment with other immunosuppressive regimens such as cyclophosphamide or chlorambucil plus glucocorticoids, or cyclosporine, or tacrolimus |
| **Lupus nephritis** | **Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of lupus nephritis when:**<br>• Used as add-on therapy in individuals who are refractory to at least two standard first-line treatment regimens, and initial treatment has been with any two of the following:<br>o Cyclophosphamide, azathioprine, or other immunosuppressant<br>o Glucocorticoid (in addition to the above) |

| Condition | Medical Necessity |
|---|---|
| **Ruxience and Truxima are subject to review for site of service administration.** | |
| **Neuromyelitis optica spectrum disorders (NMOSD)** | **Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of neuromyelitis optica spectrum disorders (NMOSD) when the following are met:**<br>• The individual has a documented diagnosis of NMOSD confirmed by:<br>  ○ At least one of the following core clinical characteristics:<br>  ▪ Optic neuritis<br>  ▪ Acute myelitis<br>  ▪ Area postrema syndrome: Episode of otherwise unexplained hiccups or nausea and vomiting<br>  ▪ Acute brainstem syndrome<br>  ▪ Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions<br>  ▪ Symptomatic cerebral syndrome with NMOSD-typical brain lesions<br>**AND**<br>  ○ Exclusion of alternative diagnoses (e.g., multiple sclerosis) |
| **Primary Sjögren syndrome** | **Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of primary Sjögren syndrome when:**<br>• Used for individuals refractory to ALL of the following:<br>  ○ Glucocorticoids<br>  ○ Other immunosuppressive agents (e.g., hydroxychloroquine or methotrexate)<br>  ○ One of the following drugs:<br>  ▪ Cyclophosphamide<br>  ▪ Mycophenolate<br>  ▪ Azathioprine |
| **Systemic lupus erythematosus (SLE)** | **Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of systemic lupus erythematosus (SLE) when:**<br>• Used as add-on therapy therapy<br>**AND** |

| Condition | Medical Necessity |
|---|---|
| **Ruxience and Truxima are subject to review for site of service administration.** | |
| | • The individual has a diagnosis of SLE confirmed using either the American College of Rheumatology (**ACR** or **EULAR/ACR**) or Systemic Lupus International Collaborating Clinics (**SLICC**) criteria<br>**AND**<br>• Has failed a 6-months trial of standard induction therapy with mycophenolate, cyclophosphamide, azathioprine, or other immunosuppressant, plus glucocorticoid |
| **Systemic sclerosis (scleroderma)** | **Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of systemic sclerosis when:**<br>• Used for individuals refractory to first-line treatment with cyclophosphamide or glucocorticoids. |
| **Autoimmune Dermatologic Diseases** | |
| **Pemphigoid diseases:**<br>• **Bullous pemphigoid**<br>• **Mucous membrane pemphigoid (including ocular cicatricial pemphigoid)**<br>• **Epidermolysis bullosa acquisita**<br><br>**Pemphigus diseases:**<br>• **Pemphigus vulgaris**<br>• **Pemphigus foliaceus**<br>• **Paraneoplastic pemphigus** | **Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of pemphigoid diseases in treatment-refractory individuals when:**<br>• Standard initial treatment was tried and failed. Standard initial treatment includes at least two of the following:<br>  ○ Glucocorticoids, azathioprine, mycophenolate, or dapsone<br><br>**Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary as a first line treatment in patients newly diagnosed with a pemphigus disease.** |
| **Hematologic** | |
| **Autoimmune hemolytic anemias (AIHA)**<br>• **Warm AHIA**<br>• **Cold AHIA** | **Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of autoimmune hemolytic anemias (AIHA) when:**<br>• Used to treat warm AIHA in glucocorticoid-refractory or glucocorticoid–dependent patients<br>**OR**<br>• Used to treat cold agglutinin disease (CAD) |

| Condition | Medical Necessity |
|---|---|
| **Ruxience and Truxima are subject to review for site of service administration.** | |
| **Chronic graft-versus-host disease (GVHD)** | **Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of chronic GVHD when:**<br>• Used in refractory to glucocorticoids |
| **Desensitization of human leukocyte antigen (HLA)** | **Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for renal transplant candidates when:**<br>• Used in desensitization of HLA-sensitized renal transplant candidates prior to transplantation |
| **Hemophilia** | **Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary in the treatment of hemophilia when:**<br>• Used as a factor inhibitor for patients who are refractory to conventional first-line treatments (e.g., immune tolerance induction, glucocorticoids with or without cyclophosphamide).<br>**AND**<br>• Used as an add-on therapy |
| **Idiopathic (immune) thrombocytopenic purpura (ITP)** | **Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary as second-line therapy for the treatment of ITP when:**<br>• The individual's platelet counts continue to be at or less than 30,000 after first-line treatment using any **one** of the following:<br>  ○ IVIG<br>  ○ High-dose glucocorticoids<br>  ○ Anti-D immunoglobulin |
| **Thrombotic thrombocytopenic purpura (TTP)** | **Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of TTP when:**<br>• Used in individuals with refractory or relapsed disease (i.e., lack of response to plasma exchange therapy and glucocorticoids) |
| **Other** | |
| **Multicentric Castleman disease (angiofollicular lymph node hyperplasia)** | **Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs) may be considered medically necessary for the treatment of multicentric Castleman disease.** |

| Second Line Products | |
|---|---|
| **Riabni (rituximab-arrx) and Rituxan (rituximab) are subject to review for site of service administration.** | |
| **Second-line agents:**<br>• **Riabni (rituximab-arrx)**<br>• **Rituxan (rituximab)**<br>• **Rituxan Hycela (rituximab and hyaluronidase human)** | **Riabni (rituximab-arrx), Rituxan (rituximab-pvvr), and Rituxan Hycela (rituximab and hyaluronidase human) may be considered medically necessary as a second-line agent in the treatment of the indications listed below when:**<br>• The individual has met the medical necessity criteria for the requested indication<br>**AND**<br>• Has had an inadequate response to or intolerance to Ruxience (rituximab-pvvr) or Truxima (rituximab-abbs)<br>○ **Exception:** An exception may be granted for Rituxan Hycela (rituximab and hyaluronidase human) when documentation is provided of difficult venous access.<br><br>**Covered Indications:**<br>• Autoimmune hemolytic anemias (AIHA)<br>• Chronic Graft-Versus-Host Disease<br>• Cryoglobulinemic Vasculitis Associated with Hepatitis-C Virus (HCV)<br>• Desensitization of Human Leukocyte Antigen (HLA)<br>• Eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome)<br>• Hemophilia<br>• Idiopathic Membranous Nephropathy<br>• Idiopathic Thrombocytopenic Purpura<br>• Lupus Nephritis<br>• Microscopic Polyangiitis<br>• Multicentric Castleman Disease<br>• Neuromyelitis Optica Spectrum Disorder (NMOSD)<br>• Pemphigoid Diseases<br>• Pemphigus Diseases<br>• Primary Sjögren Syndrome<br>• Rheumatoid Arthritis (RA)<br>• Systemic Lupus Erythematosus (SLE)<br>• Systemic Sclerosis (scleroderma) |

| Second Line Products | |
|---|---|
| **Riabni (rituximab-arrx) and Rituxan (rituximab) are subject to review for site of service administration.** | |
| | • Thrombotic Thrombocytopenic Purpura (TTP)<br>• Wegener's Granulomatosis |

| Drug | Investigational |
|---|---|
| **Rituximab Products** | **Rituximab is investigational for all other non-oncologic uses, including but not limited to:**<br>• Induction immunosuppressive therapy for kidney transplantation<br>• Induction immunosuppressive therapy for heart transplantation<br>• Mixed connective tissue disease<br>• Multiple sclerosis<br>• Paroxysmal cold hemoglobinuria<br>• Prophylaxis for graft-versus-host disease<br>• Treatment of antibody-mediated rejection after pancreatic islet transplantation<br>• Treatment of antibody-mediated rejection in solid organ transplant recipients<br>• Treatment of minimal change disease<br>• Treatment of myasthenia gravis<br><br>**All other uses of rituximab products for conditions not outlined in this policy are considered investigational.**<br><br>**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.** |

| Length of Approval | |
|---|---|
| **Approval** | **Criteria** |
| **Initial authorization** | **Non-formulary exception reviews for rituximab products listed in this policy may be approved up to 12 months.** |

| Length of Approval | |
|---|---|
| **Approval** | **Criteria** |
| | **All other reviews for rituximab products listed in this policy may be approved up to 6 months.** |
| **Re-authorization criteria** | **Non-formulary exception reviews and all other reviews for rituximab products listed in this policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.** |

| Documentation Requirements |
|---|
| **The individual's medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of:**<br>• Diagnosis/condition<br>• History and physical examination documenting the severity of the condition<br>• Prior treatment (if any)<br>• If service is requested at an outpatient hospital-based setting, supporting documentation for why infusion cannot be performed at physician's office, patient's home, or an infusion center |

## Coding

| Code | Description |
|---|---|
| **HCPCS** | |
| J3590 | Unclassified biologics (use to report Amjevita , Cyltezo, Hyrimoz HCF, Sandoz, Simlandi) |
| J9311 | Injection, rituximab 10 mg and hyaluronidase (Rituxan Hycela) |
| J9312 | Injection, rituximab (Rituxan), 10 mg |
| Q5115 | Injection, rituximab-abbs, biosimilar, (Truxima), 10mg |
| Q5119 | Injection, rituximab-pvvr, biosimilar, (Ruxience), 10 mg |
| Q5123 | Injection, rituximab-arrx, biosimilar, (Riabni), 10 mg |

## Related Information

### Dosing

Rituxan (rituximab) should be administered by a healthcare professional with appropriate medical support to manage severe and potentially fatal infusion reactions (Biogen & Genentech, 2020).

### Pregnancy

Based on human data, rituximab can cause adverse developmental outcomes including B-cell lymphocytopenia in infants exposed to rituximab in-utero. In animal reproduction studies, intravenous administration of rituximab to pregnant cynomolgus monkeys during the period of organogenesis caused lymphoid B-cell depletion in the newborn offspring at doses resulting in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated populations is unknown. The estimated background risk in the US general population of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies. Advise pregnant women of the risk to a fetus.

### Children

The age described in this policy for Site of Service reviews for medical necessity is 13 years of age or older. The age criterion is based on the following: Pediatric patients are not small adults. Pediatric patients differ physiologically, developmentally, cognitively, and emotionally from adult patients, and vary by age groups from infancy to teen. Children often require smaller doses than adults, lower infusion rates, appropriately sized equipment, the right venipuncture site determined by therapy and age, and behavioral management during administration of care. Specialty infusion training is therefore necessary for pediatric IV insertions and therapy. Due to pediatric unique physiology and psychology, this policy is limited to patients above the age of 13.

# Evidence Review

## Description

Rituxan (rituximab) is a monoclonal antibody against the CD20 antigen on B lymphocytes. Rituximab lyses pre-B and B lymphocytes and is successfully used to treat B-cell lymphoma. Rituximab has been used with increased frequency for nononcologic indications, particularly autoimmune diseases thought to be B-cell mediated.

## Background

## Rituxan (rituximab)

Rituxan (rituximab) 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 lysis of normal and malignant CD20-expressing B cells; possible mechanisms of cell lysis include complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity.[1]

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.

Rituximab is infused intravenously.

## Adverse Events

Rituxan (rituximab) carries the following black box warnings[2]:

- 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

Labelled 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
- Embryo-fetal toxicity

Adverse events that occurred in at least 10% of patients in pivotal rheumatoid arthritis trials included upper respiratory tract infection, nasopharyngitis, urinary tract infection, and bronchitis.

Adverse events that occurred in at least 15% of patients in the pivotal Wegener granulomatosis and microscopic polyangiitis study included infections, nausea, diarrhea, headache, muscle spasms, anemia, and peripheral edema.

## Summary of Evidence

## Food and Drug Administration–Approved Uses

**Rheumatoid Arthritis (FDA label)**

For individuals who have moderately to severely active rheumatoid arthritis and inadequate response to one or more standard agents (eg, tumor necrosis factor inhibitors, inadequate response to methotrexate or other conventional synthetic disease-modifying antirheumatic drug) who receive rituximab and methotrexate, the evidence includes 4 RCTs and observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Compared with methotrexate alone, rituximab improved disease-related outcomes consistent with an improved benefit-risk profile. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Subsequent publications have confirmed this finding. A 5-year extension study reported sustained improvements in clinical and radiographic outcomes in patients who received at least 1 course of rituximab compared with placebo, although differences in progression of structural damage were not statistically significant. Observational studies have suggested switching to rituximab after failing 1 TNF inhibitor may be more efficacious than switching to another TNF inhibitor. Evidence for the use of rituximab in TNF inhibitor–naive patients is lacking. For patients with an inadequate response to MTX and contraindications to TNF inhibitor therapy, rituximab may be a reasonable option. In the 5-year extension study, adverse event rates were generally stable over time.

**Antineutrophil Antibody –Associated Vasculitides (Granulomatosis with polyangiitis and microscopic polyangiitis)- (FDA Label)**

Granulomatosis with polyangiitis (GPA; Wegener granulomatosis), microscopic polyangiitis (MPA), and Churg-Strauss syndrome are classified as antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides because most patients with generalized disease have antibodies against proteinase 3 (PR3) or myeloperoxidase (MPO), enzymes found in neutrophil granulocytes.[152] Each vasculitis can be distinguished by the predominant type of immunofluorescence staining pattern (antibody) present, eg, cytoplasmic ANCA (anti-PR3) in GPA and perinuclear ANCA (anti-MPO) in MPA. These vasculitides are also considered pauci-immune because, unlike immune complex vasculitides, they are not characterized by immune complex deposition.[153] ANCA-associated vasculitides affect small-to-medium-size blood vessels, particularly in the respiratory tract and kidneys; the characteristic kidney lesion is pauci-immune focal and segmental necrotizing and crescentic glomerulonephritis.[154] Limited vasculitis may respond to MTX plus glucocorticoids; standard treatment for more severe disease is cyclophosphamide plus glucocorticoids. Finally, these conditions are uncommon. The prevalence of GPA in the United States is estimated at 32 per million and MPA 2.9 per million.[155]

For individuals who have antineutrophil cytoplasmic antibody–associated vasculitides (granulomatosis with polyangiitis and microscopic polyangiitis) who receive rituximab and glucocorticoids, the evidence includes evidence from 3 RCTs and observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Compared with a cyclophosphamide regimen, rituximab improved disease-related outcomes consistent with an improved benefit-risk profile (this was accomplished over the course of two trials). In 1 trial, rituximab maintenance was superior to an azathioprine regimen but accompanied by considerable uncertainty. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

One double-blind, double-dummy RCT demonstrated the noninferiority of rituximab to cyclophosphamide in patients with newly diagnosed or relapsing severe GPA (formerly called Wegener granulomatosis) or MPA. Both treatments were administered in combination with glucocorticoids. More patients who received a single course of rituximab maintained complete remission for 12 and 18 months compared with patients who continued azathioprine maintenance therapy, although these differences were not statistically significant. An open-label RCT in patients with newly diagnosed ANCA (GPA or MPA)-associated nephropathy showed no difference in sustained remission or serious adverse events at 12 months in patients treated with or without a rituximab-containing induction regimen. One trial found rituximab of similar efficacy in maintaining remission compared with an azathioprine regimen.

**Pemphigoid and Pemphigus Diseases (FDA Label)**

Pemphigoid diseases include 8 blistering disorders characterized by auto-antibodies directed against the epidermal basement membrane: bullous pemphigoid, mucous membrane pemphigoid, pemphigoid gestationis, linear IgA disease, epidermolysis bullosa acquisita, anti-laminin g1/anti-p200 pemphigoid, lichen planus pemphigoides, and pemphigoid with renal insufficiency. Pemphigus, in contrast, comprises 3 major forms characterized by auto-antibodies directed against epidermal cell junctions: pemphigus vulgaris, pemphigus foliaceus, and paraneoplastic pemphigus. Both classes of disease are characterized by blisters and erosions; however, pemphigoid blisters are subepidermal and therefore tense, and pemphigus blisters are more superficial and therefore flaccid or often ruptured. Nikolsky sign—exfoliation and blister formation with skin friction—is negative in pemphigoid diseases and positive in pemphigus.[156]

The evidence on first-line treatment with rituximab plus corticosteroids in patients with newly diagnosed pemphigus consists of an RCT and small case series. The RCT found that patients treated with rituximab plus short-term corticosteroids (3-6 months) had significantly better outcomes than those treated with long-term corticosteroid use. Outcomes included the complete response rate, cumulative dose of corticosteroids, and rate of grade 3 or 4 serious adverse events.

Evidence for rituximab in pemphigoid and pemphigus diseases comprises case reports, case series, and 1 retrospective comparative study in ocular cicatricial pemphigoid. Patients were refractory to previous treatments, but most (75%-100%) responded to rituximab. Infections, including serious and fatal infections, were reported in 4% to 19% of patients, but AE reporting may have been incomplete. Only 3 of 8 pemphigoid diseases were examined in the literature: epidermolysis bullosa acquisita, bullous pemphigoid, and mucous membrane pemphigoid. Although the body of evidence is small, disease progression can lead to serious outcomes (e.g.,

blindness) or death, reported response rates were high, and treatment options in refractory patients are limited. For these reasons, rituximab may be considered medically necessary for treatment of the pemphigoid and pemphigus diseases reviewed in the literature in treatment-refractory patients.

## Food and Drug Administration–Off-Label Covered Uses

## Hematologic Disorders and Vasculitides

### Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia (AIHA) comprises direct Coombs-positive anemias, such as warm (80% of AIHA) and cold autoantibody types, and drug-induced AIHA. Warm AIHA is mediated by warm-reactive antibodies, primarily immunoglobulin G (IgG), that react optimally with human red blood cells in vitro at 37°C (98.6°F). Cold-reactive antibodies, primarily IgM, react maximally at 4°C (39°F). Cold AIHA, in turn, comprises cold agglutinin syndrome and paroxysmal cold hemoglobinuria. Warm and cold AIHA may be idiopathic (primary) or secondary, eg, to lymphoma or lymphoproliferative disorders. Glucocorticoids and splenectomy are currently used to treat AIHA refractory to first-line therapy. Corticosteroids are first-line treatment in warm AIHA but less effective in cold AIHA.[3,4]

Rituximab is not considered a treatment option for paroxysmal cold hemoglobinuria due to the generally self-limiting course and excellent prognosis of this disorder.

For individuals who have AIHA—warm AIHA and cold agglutinin syndrome—refractory to first-line therapy who receive rituximab, the evidence includes RCTs and observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Two RCTs have found that overall response rates were better with rituximab than a control condition at 1 year in patients with newly diagnosed warm AIHA. Serious adverse events were higher with rituximab than corticosteroids (1 RCT) but lower than placebo (the other RCT). Response rates from observation studies have supported these findings and found lesser yet substantive response rates in patients with cold agglutinin syndrome. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

### Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura (ITP) is an acquired autoimmune disorder with no known cause, although it can co-occur with other autoimmune diseases. Corticosteroids, intravenous immunoglobulins (IVIG), or anti-Rho(D) immunoglobulin are standard initial treatments. However, relapses are common within the first year, and splenectomy is often required. Rituximab has been investigated to delay or avoid splenectomy, especially in children.[10,11] For individuals who have relapsed or refractory ITP who receive rituximab, the evidence includes an RCT of second-line therapy and observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Rituximab as second-line treatment for adult thrombocytopenia trial failed to demonstrate improved outcomes with rituximab as second-line therapy in adults with ITP. The evidence is insufficient to determine the effects of the technology on health outcomes.

### Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening condition characterized by microvascular thrombosis, thrombocytopenia, and microangiopathic hemolytic anemia leading to end-organ ischemia and infarction (commonly brain, heart, kidneys).[15] TTP is due to an acquired (95% of cases) or congenital (5% of cases) deficiency of the von Willebrand factor–cleaving protease, ADAMTS13. In 38% to 95% of cases of idiopathic TTP, anti-ADAMTS13 neutralizing antibodies are present.[16] When ADAMTS13 is absent or depleted, large uncleaved von Willebrand factor multimers aggregate in high shear areas of the microvasculature, leading to thrombotic microangiopathy.[17] The main treatment for TTP is plasma exchange (PE) and corticosteroids. Refractory TTP, defined as progression of clinical symptoms during PE therapy, occurs in 10% to 20% of acquired TTP cases.[18] For these patients, increased PE and/or addition of cyclosporine are current treatment options.[17]

For individuals who have relapsed or refractory TTP who receive rituximab, the evidence includes a nonrandomized trial (phase 2), a cohort study, and case series. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. These studies have provided consistent evidence of improved health outcomes. For example, a phase 2 trial reported substantially lower relapse rates than historical controls. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

### Factor Inhibitors in Hemophilia

Hemophilia is a coagulopathy characterized by reduced, absent, or nonfunctioning clotting factor VIII (FVIII) (hemophilia A) or, less commonly, factor IX (hemophilia B). Treatment comprises replacement therapy with the missing or deficient clotting factor. Over time, antibodies to infused clotting factor develop in 20% to 30% of patients with severe hemophilia A and 2% to 5% of patients with hemophilia B.[28] If left untreated, antibody inhibitors eventually render replacement therapy ineffective. Immune tolerance induction (ITI) is recommended first-line treatment of factor inhibitors in hemophilia.[30] ITI comprises increasing the dose and frequency of factor infusions until inhibitor is undetectable and FVIII levels normalize. Success rate is low (25%), and associated risks (e.g., anaphylaxis, irreversible nephrotic syndrome) are significant. Immunosuppressive therapy with corticosteroids alone or in combination with cyclophosphamide is recommended for first-line inhibitor eradication. Rituximab has been investigated as an alternative to ITI or for patients who are nonresponsive to ITI.

Hemophilia is generally considered a genetic disorder but acquired hemophilia A is a rare autoimmune disease caused by acquired auto-antibodies against FVIII. Underlying medical conditions, such as autoimmune diseases, solid tumors, lymphoproliferative malignancies, or pregnancy, can be identified in approximately half of patients. Immunosuppressive therapy with corticosteroids alone or in combination with cyclophosphamide is recommended for first-line inhibitor eradication. Rituximab has been studied as second-line treatment in this setting.[29]

For individuals who have congenital or acquired hemophilia A with inhibitory antibodies, refractory to first-line therapy, who receive rituximab, the evidence includes a phase 2 trial, a cohort study, and case series. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Response rates have varied among reports (25% to 50%), depending on whether rituximab was administered as mono- or combination therapy; remission rates have generally been high. Treatment-related adverse events—some severe—have been reported. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

## Autoimmune-Related Connective Tissue Disorders

### Mixed Connective Tissue Disease

Mixed connective tissue disease (MCTD) has various features of systemic lupus erythematosus (SLE), systemic sclerosis, polymyositis/dermatomyositis (PM/DM), and rheumatoid arthritis (RA) in the presence of increased anti-ribonucleoprotein (anti-RNP) antibodies.[41] Although some have questioned whether MCTD is a distinct entity, associated human leukocyte antigen (HLA)

class 2 alleles (HLA-DR4 and -DR1) are distinct from those associated with SLE, systemic sclerosis, and PM/DM. The most common clinical presentation—Raynaud syndrome, arthralgias, swollen hands, sausage-like fingers, and muscle weakness—appear in 90% of patients. More serious organ involvement can lead to pulmonary arterial hypertension, glomerulonephritis, gastrointestinal bleeding, and severe central nervous system involvement. Common treatments include corticosteroids and cyclophosphamide.

For individuals who have MCTD who receive rituximab, the evidence includes 2 case series. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. In one of the series, 3 of 5 patients with MCTD achieved partial remission with rituximab and, in the other, which focused on MCTD related to interstitial lung disease, there was no significant change in forced vital capacity at 1 or 2 years after initiating rituximab. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Multicentric Castleman Disease**

Castleman disease (angiofollicular lymph node hyperplasia) is a rare lymphoproliferative disorder associated with human herpes virus–8 infection. Prevalence is increased among HIV-infected patients and associated with Kaposi sarcoma. Progression to lymphoma and mortality is high in these patients. Castleman disease has two distinct forms with characteristic findings on histologic examination: unicentric or localized (hyaline vascular histology), and multicentric (plasma cell infiltrate). The clinical presentation typically involves lymphadenopathy and multiorgan involvement with an aggressive course. In HIV-non-infected patients, multicentric Castleman disease typically presents after age 70 years.[44] For HIV-infected patients, current guidelines suggest IV ganciclovir or oral valganciclovir for treatment of multicentric Castleman disease based on level C evidence. Rituximab is considered an alternative therapy.[45] Other treatments include combination chemotherapy and tocilizumab, a monoclonal anti-interleukin 6 antibody.

For individuals who have multicentric Castleman disease (angiofollicular lymph node hyperplasia) who receive rituximab, the evidence includes 2 prospective and 3 retrospective cohort studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Although the evidence base consists of nonrandomized studies, rituximab has significantly improved overall survival and markedly reduced the incidence of non-Hodgkin lymphoma. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Primary Sjögren Syndrome**

Sjögren syndrome is an autoimmune disorder characterized by lymphocytic infiltration and progressive destruction of the exocrine glands of the body, specifically the salivary and lacrimal glands, which cause xerostomia (dry mouth) and keratoconjunctivitis sicca (dry eyes). Extraglandular disease leads to vaginal dryness, chronic bronchitis, and dry skin, and may affect the kidneys, blood vessels, liver, pancreas, peripheral nervous system (distal axonal sensorimotor neuropathy), and central nervous system. Sjögren syndrome often accompanies other autoimmune disorders, such as RA and lupus. The condition is most common in women older than 40 years. Therapies that are currently being used to treat Sjögren syndrome include MTX, hydroxychloroquine, infliximab, etanercept, azathioprine, mycophenolate mofetil (MMF), cyclophosphamide, and glucocorticoids.

For individuals who have primary Sjögren syndrome, refractory to first-line therapy, who receive rituximab, the evidence includes a large RCT (disease onset <10 years prior) and smaller observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The efficacy of rituximab has not been consistently demonstrated in this population. For example, a large (N=120) randomized trial showed no difference in response rates compared with placebo, and a small (N=41) nonrandomized trial showed statistically significant differences in response rates compared with disease-modifying antirheumatic drugs in previously treated patients. The incidence of adverse events did not appear to increase above that observed in other patient populations. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Systemic Lupus Erythematosus**

For individuals who have SLE, refractory to first-line therapy, who receive rituximab, the evidence includes a large RCT and systematic reviews that also included observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The single RCT failed to show improved response rates at 1 year with rituximab add-on therapy. Cohort studies and case series of refractory patients have generally reported higher response rates than controlled studies. Therapies currently being used to treat SLE refractory to first-line therapy include MTX, hydroxychloroquine, belimumab, etanercept, azathioprine, MMF, cyclophosphamide, cyclosporine, and glucocorticoids. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Lupus Nephritis**

Lupus nephritis (LN) is among the most serious complications of SLE. It occurs in approximately half of SLE patients and is associated with a poor prognosis.[65] Estimated 5-year survival among patients with International Society of Nephrology/Renal Pathology Society class IV (diffuse) LN is 80% and among all SLE patients, 86%[66]; 5% to 10% of LN patients will progress to end-stage renal disease at 10 years.[67] Therapies currently being used to treat lupus nephritis include glucocorticoids, cyclophosphamide, MMF, cyclosporine, tacrolimus, and belimumab. Treatment regimens including cyclophosphamide or MMF are administered with corticosteroids. Response rates at 1 year are 50% to 80%, but they are often only partial responses.

For individuals who have lupus nephritis, refractory to first-line therapy, who receive rituximab, the evidence includes an RCT and noncomparative studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The single RCT did not show improved response rates at 1 year with rituximab add-on therapy. Noncomparative studies have reported complete and partial response rates of 30% to 40% and approximately 35%, respectively, in patients with mostly refractory disease. Adverse events occurred in approximately 20% of patients. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Systemic Sclerosis (Scleroderma)**

The purpose of rituximab in patients who have systemic sclerosis (scleroderma), refractory to first-line therapy, is to provide a treatment option that is an alternative to or an improvement on existing therapies. Therapies that are currently being used to treat systemic sclerosis include MMF, cyclophosphamide, and cyclosporine. For individuals who have systemic sclerosis, refractory to first-line therapy, who receive rituximab, the evidence includes observational studies and a small, unblinded trial. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Add-on rituximab therapy has generally improved skin symptoms and pulmonary function tests; adverse events, including sepsis deaths, occurred in 21% to 47% of patients. Long-term follow-up for efficacy and safety is limited. The evidence is insufficient to determine the effects of the technology on health outcomes.

## Other Autoimmune-Related Conditions and Disorders

### Churg-Strauss Syndrome

Churg-Strauss syndrome, also called eosinophilic granulomatosis with polyangiitis (EGPA), is an anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis characterized by peripheral and tissue eosinophilia, frequently affecting the lungs, in patients with asthma.[21] The disease is uncommon, with an estimated prevalence of 11 to 14 per million adults. Eosinophilic infiltration of the heart, lungs, and kidneys can lead to ventricular dysfunction, pulmonary hemorrhage, and renal failure, respectively; cardiac involvement is the leading cause of early death. Treatment recommendations are based primarily on studies in other ANCA-associated vasculitides (GPA and MPA). Corticosteroids are used with or without cyclophosphamide, depending on disease severity. Azathioprine or MTX may be used as steroid-sparing agents. Because of its demonstrated efficacy in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), rituximab has been used in patients with EGPA syndrome refractory to conventional immunosuppressant therapy.[22]

For individuals who have Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis) who receive rituximab, the evidence includes a single-center retrospective observational study and 3 case series. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Response and remission rates have generally been high, but treatment-related adverse events—some severe—have been reported. The evidence is insufficient to determine the effects of the technology on health outcomes.

### Hepatitis C Virus–associated Cryoglobulinemic Vasculitis

Of 3 types of cryoglobulinemia, type 2 and type 3 may be called "mixed" due to the clonal expansion of more than 1 immunoglobulin class, commonly IgM and IgG. (Type 1, in contrast, is characterized by a single monoclonal immunoglobulin.) Eighty percent of mixed cryoglobulinemic vasculitis is associated with chronic hepatitis C virus (HCV) infection. Treatment of the underlying infection to achieve sustained viral response is the treatment of choice. For patients who do not achieve sustained viral response, corticosteroids and cytotoxic agents are alternative treatment options but may exacerbate underlying liver disease.[34,35]

For individuals who have HCV-associated cryoglobulinemic vasculitis who receive rituximab, the evidence includes 2 RCTs, a phase 2 nonrandomized trial, and observational studies. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The reported response rates in these studies are consistent with

improved health outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

### *Multiple Sclerosis*

The purpose of rituximab in patients who have multiple sclerosis (MS) is to provide a treatment option that is an alternative to or an improvement on existing therapies. Therapies that are currently being used to treat MS include interferons, glatiramer acetate, teriflunomide, fingolimod, dimethyl fumarate, alemtuzumab, mitoxantrone, and natalizumab.

For individuals who have MS who receive rituximab, the evidence includes 2 RCTs, a registry study, and case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. One RCT in patients with relapsing-remitting MS showed reductions in the number of lesions detected by gadolinium-enhanced magnetic resonance imaging at 24 and 48 weeks, and in clinical outcomes at 24-week follow-up. However, methodologic limitations restrict the conclusions drawn from these data. One well-designed RCT in patients with primary-progressive MS demonstrated no effect of rituximab on disease progression. A large registry study found that rituximab was associated with a relatively low rate of adverse events and relapses and little change in disability scores; this study lacked a comparison group. The evidence is insufficient to determine the effects of the technology on health outcomes.

### Neuromyelitis Optica

Neuromyelitis optica (NMO) is a rare autoimmune inflammatory disorder that selectively affects the spinal cord and optic nerves; clinical presentation is characterized by severe optic neuritis that can lead to blindness and transverse myelitis that can lead to paralysis. The clinical course typically is more severe than in MS, and often fatal,[97] and treatments may differ.[98, 99] An autoantibody to aquaporin-4, a water channel found in high concentrations at the blood-brain barrier, is included in NMO diagnostic criteria.[100,101] Curative treatment does not currently exist; treatment goals are: relapse remission, relapse prevention, and symptom relief.[102] Immunosuppression with azathioprine or mycophenolate mofetil (MMF) is commonly used for relapse prevention. Therapies currently used to treat NMO include azathioprine, MMF, methotrexate, mitoxantrone, and glucocorticoids. Rituximab is being studied for relapse prevention in NMO.

For individuals who have NMO (prevention relapse), refractory to first-line therapy, who receive rituximab, the evidence includes uncontrolled observational studies and systematic reviews. Relevant outcomes are symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. A 2016 systematic review of 46 uncontrolled studies found significant reductions in the relapse rate and Expanded Disability Status Scale scores after beginning treatment with rituximab. Based on adverse events reported, the safety of rituximab in NMO appeared comparable to the safety in other patient populations. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

***Myasthenia Gravis***

Myasthenia gravis is a chronic autoimmune disorder that affects the neuromuscular junction resulting in varying degrees of muscular weakness. The normal communication of nerve impulses involves nerve endings releasing acetylcholine, a neurotransmitter at the neuromuscular junction, which normally binds with acetylcholine receptors that activate and result in a muscle contraction. For individuals with myasthenia gravis, this cholinergic communication is disrupted by antibodies.

For individuals who have refractory and nonrefractory myasthenia gravis who receive rituximab, the evidence includes observational studies and a systematic review. Relevant outcomes are change in disease status, quality of life, and treatment-related morbidity. A systematic review found a significant reduction in a myasthenia gravis symptom score after beginning rituximab treatment and a relatively low rate of adverse events. A limitation of the studies was that adverse event reports were not available for all patients. An uncontrolled observational study found significantly better clinical outcomes in patients with anti-MuSK myasthenia who were treated with rituximab compared with those who did not receive rituximab. However, few controlled studies and no RCTs are available. The evidence is insufficient to determine the effects of the technology on health outcomes.

***Idiopathic Membranous Nephropathy***

Membranous nephropathy involves the abnormal thickening of the glomerular basement membrane and is a leading cause of nephrotic syndrome. Most membranous nephropathy cases occur from unknown causes, and secondary membranous nephropathy may result from other predisposing diseases, infection, or medical therapy. In many cases, conservative treatment with renin-angiotensin system blockade is provided. Immunomodulatory therapies (e.g., alkylating

agents, calcineurin inhibitors, corticosteroids) are used to treat individuals who are unresponsive to conservative therapy. Rituximab has been evaluated in patients with idiopathic membranous nephropathy who have failed previous treatment with other immunosuppressive regimens or those with a moderate risk of progression who have not previously received immunosuppressive therapy.

For individuals who have idiopathic membranous nephropathy who receive rituximab, the evidence includes an RCT and observational studies. Relevant outcomes are change in disease status, quality of life, and treatment-related morbidity. Rituximab may have moderate benefit in patients with idiopathic membranous nephropathy who have failed previous treatment with other immunosuppressive regimens or those with a moderate risk of progression who have not previously received immunosuppressive therapy. However, an RCT with longer follow-up is needed to confirm the benefits of rituximab and to determine the optimal schedule, dose, and long-term safety and efficacy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

#### *Minimal Change Disease*

For individuals who have minimal change in disease (adults and children) who receive rituximab, the evidence includes observational studies in adults and 2 RCTs and observational studies in children. Relevant outcomes are change in disease status, quality of life, and treatment-related morbidity. Rituximab benefit children with nephrotic syndrome associated with minimal change disease. However, because of the risk of severe and potentially life-threatening complications, rituximab use should be restricted to children with frequent relapses and serious adverse events from their medications (because the long-term efficacy and safety of rituximab in this group of patients remain unclear). The evidence is insufficient to determine the effects of the technology on health outcomes.

## Transplant-Related Conditions and Disorders

### Glucocorticoid-Refractory Chronic Graft-Versus-Host Disease (GVHD)

Chronic GVHD, historically defined as occurring more than 100 days after transplant,[128] is the primary cause of late morbidity and mortality after allogeneic hematopoietic cell transplantation.[129] Approximately half of the patients respond to first-line treatment (systemic corticosteroid with or without a calcineurin inhibitor), but treatment options for steroid-refractory disease are limited, and the prognosis is poor. Therapies currently being used to treat

glucocorticoid-refractory chronic GVHD include MMF, cyclophosphamide, and cyclosporine. For individuals who have corticosteroid-refractory chronic GVHD who receive rituximab, the evidence includes multiple cohort studies. Relevant outcomes are change in disease status, quality of life, and treatment-related morbidity. Treatment with rituximab has demonstrated response rates in most patients, with sustained response and steroid reduction or discontinuation in some. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Pretransplant HLA Desensitization in Kidney Transplantation.**

Patients who are HLA-sensitized have broadly reactive alloantibodies (e.g., due to previous pregnancy, transfusion of blood or blood products, or transplantation). HLA-sensitized patients are difficult to match for donor organs because of the high risks of hyperacute rejection and graft loss with cross-matched organs (i.e., positive for reactive antigens). Panel reactive antibody (PRA) assays define the level of HLA sensitization and are used to optimize identification of compatible donors. Some transplant centers employ desensitization protocols to overcome HLA sensitization. Protocols commonly use low-dose IVIG with PE or high-dose IVIG.[135]

Several cohort studies in sensitized individuals demonstrated good patient and graft survival with rituximab desensitization 3 years after transplant. An RCT comparing desensitization regimens with and without rituximab was terminated due to excess SAEs in the control arm, and 1 study reported no increase in polyomavirus BK-associated nephropathy at 2-year follow-up. This evidence suggests that health outcomes are improved with rituximab desensitization regimens in sensitized renal transplant candidates, therefore this is a covered indication.

**Kidney and Heart Transplant Candidates Receiving Induction Immunosuppression**

Antibodies other than anti-HLA antibodies that are circulating in the planned transplant recipient may cause damage to the donor organ. Antibody-mediated injury to allografts comprises ABMR, ABMR without complement deposition, antibody-mediated endarteritis, and accelerated arteriosclerosis of allografts.[141] Induction immunosuppressive regimens initiated before, at the time of, or immediately after transplantation, mute T-cell responses to antigen presentation reduces acute rejection.[142] Therapies that are currently being used to treat patients with heart or kidney transplant who are receiving induction include immunosuppressive antibodies, basiliximab, and alemtuzumab. Rituximab as part of a combination induction regimen that typically includes plasmapheresis and IVIG therapy such as antithymocyte globulin recessive agents is being considered.

For individuals who are kidney transplant candidates who are receiving induction immunosuppressive therapy, the evidence includes cohort studies with historical controls and case series RCTs and systematic reviews. Although observed improvements in outcomes have suggested potential benefit with rituximab, data are retrospective or from small prospective studies. Dose-response studies and larger RCTs with longer follow-up are needed to demonstrate improved health outcomes. For individuals who are heart transplant candidates who are receiving induction immunosuppressive therapy, the recommendation for the use of rituximab as part of a combination regimen is based on consensus reporting of case reports and expert opinion.

***Antibody-Mediated Rejection of a Solid Organ Transplant***

Therapies currently being used to treat patients with ABMR of a solid organ transplant include immunosuppression, plasmapheresis or PE, IVIGs, corticosteroids, and antilymphocyte antibodies. For individuals who have ABMR of a solid organ transplant who receive rituximab, the evidence includes cohort studies with historical controls and case series. Relevant outcomes are change in disease status, quality of life, and treatment-related morbidity. Although observed improvements in outcomes have suggested potential benefit with rituximab, data are retrospective or from small prospective studies. Dose-response studies and larger RCTs with longer follow-up are needed to demonstrate improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

ABMR After Pancreatic Islet Transplantation Autoimmune destruction of insulin-secreting islet beta-cells causes type 1 diabetes.[151]ABMR after pancreatic transplantation is less common than cell-mediated rejection, but when it occurs, pancreatic islet cells appear to be particularly susceptible to injury.[152] Pancreatic islet transplantation is used in patients who have type 1 diabetes complicated by recurrent severe hypoglycemic episodes, and insulin independence is restored in 44% of patients.[153] However, graft function commonly declines over time, which is thought to be due in part to allograft rejection. Immunosuppression management after islet transplantation is not standardized. Therapies currently being used to treat ABMR after pancreatic islet cell transplantation include corticosteroids.

For individuals who have ABMR after pancreatic islet transplantation who receive rituximab, the evidence includes a case report. Relevant outcomes are change in disease status, quality of life, and treatment-related morbidity. The evidence is insufficient to determine the effects of the technology on health outcomes.

## Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in **Table 1**.

## Table 1. 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-bind, 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) |
| **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) |
| **Idiopathic membranous nephropathy** | | | |
| 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) |

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| NCT03018535 | A Randomized Controlled Trial of Rituximab Versus Steroids and Cyclophosphamide in the Treatment of Idiopathic Membranous Nephropathy (RI-CYCLO) | 76 | Dec 2019 |
| **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 |

ANCA: antineutrophil cytoplasmic antibody; NCT: national clinical trial.

[a] Industry sponsored or co-sponsored.

## Clinical Input Received From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 9 physician specialty societies (16 reviewers) and 1 academic medical center while this policy was under review in 2014. Overall, input supported the policy statements as written. Exceptions included Churg-Strauss syndrome (most reviewers considered rituximab medically necessary and supported first-line use [induction therapy] for severe disease) and acquired thrombotic thrombocytopenic purpura (reviewers were split). Other suggested indications were chronic inflammatory demyelinating polyneuropathy, immunoglobulin M-related demyelinating neuropathies, myasthenia gravis, Lambert-Eaton myasthenic syndrome, ABO incompatible organ/tissue grafts, and post-solid organ transplant membranous nephropathy.

## Practice Guidelines and Position Statements

## American College of Rheumatology

The American College of Rheumatology (2012) published evidence-based consensus guidelines on the treatment of lupus nephritis.[157] 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).

**Rheumatoid Arthritis**

The American College of Rheumatology updated its evidence-based consensus guidelines on rheumatoid arthritis (RA) in 2015 (updated guideline anticipated in 2021) and made the following recommendations[163]:

- If a patient has moderate (e.g., Clinical Disease Activity Index [CDAI] >10-22 or Disease Activity Score in 28 joints [DAS-28] ≥3.2 to ≤5.1) or high (e.g., CDAI >22 or DAS-28 >5.1) disease activity after 3 months of MTX monotherapy or DMARD combination therapy, the panel recommended adding (Level A evidence, based on multiple RCTs) or switching (Level C evidence, based on expert consensus, case studies, or standard-of-care) to a TNF inhibitor, abatacept, or rituximab as an alternative to DMARD combination therapy.
- If a patient still has moderate or high disease activity after 3 months of TNF inhibitor therapy and this is due to a lack or loss of benefit, switching to another TNF inhibitor or a non-TNF biologic, such as rituximab (Level B evidence, based on a single randomized trial or nonrandomized studies), is recommended.
- Reassessment after treatment with a non-TNF biologic, such as rituximab, is recommended at 6 months due to anticipation that a longer time to peak effect is needed for non-TNF biologics compared with TNF inhibitors.
- Rituximab may be started or resumed in patients with RA who have a previously-treated solid malignancy, including nonmelanoma skin cancer, within the last 5 years, or a previously-treated melanoma skin cancer or lymphoma (Level C recommendation, based on clinical trial extensions, observational data, and expert consensus).

- The panel recommended vaccination with all killed (pneumococcal, influenza intramuscular, and hepatitis B), recombinant (human papillomavirus [HPV] vaccine for cervical cancer), and live attenuated (herpes zoster) vaccines before starting a DMARD or biologic agent.
    - If not administered before starting a DMARD or biologic agent, pneumococcal (killed), influenza intramuscular (killed), hepatitis B (killed), and HPV (recombinant) vaccines should be administered to RA patients already taking a DMARD or biologic agent.
    - Live attenuated vaccines (herpes zoster) are not recommended during therapy with biologic agents.

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

An updated guideline covering recommendations for all ILDs was published in 2023. Rituximab was conditionally recommended for patients with systemic autoimmune rheumatic disease-ILD as a first-line treatment option and for those with progression despite first-line ILD treatment. Rituximab was also conditionally recommended for patients with rapidly progressive systemic autoimmune rheumatic disease-ILD.

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

## American Society of Hematology

The American Society of Hematology (2019) published evidence-based guidelines on immune thrombocytopenia (ITP).[158] Rituximab was suggested in the following clinical scenarios (all are conditional recommendations which "the guideline panel suggests…"):

- "In adults with newly diagnosed ITP, the ASH guideline panel suggests corticosteroids alone rather than rituximab and corticosteroids for initial therapy"
- "In adults with ITP lasting ≥3 months who are corticosteroid-dependent or have no response to corticosteroids, the ASH guideline panel suggests rituximab rather than splenectomy"
- "In adults with ITP lasting ≥3 months who are corticosteroid-dependent or have no response to corticosteroids, the ASH guideline panel suggests a TPO-RA rather than rituximab"
- "In children with ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL and do not respond to first-line treatment, the ASH guideline panel suggests the use of TPO-RAs rather than rituximab"
- "In children with ITP who have non–life-threatening mucosal bleeding and/or diminished HRQoL and do not respond to first-line treatment, the ASH guideline panel suggests rituximab rather than splenectomy"

## *American Thoracic Society*

In 2023, the American Thoracic Society (ATS) published guidelines for the treatment of systemic sclerosis-associated ILD (SSc-ILD). The authors provided a conditional recommendation for the use of rituximab (among other immunosuppressants) based on very low-quality evidence. Authors also noted that: "Further research is needed to determine the most optimal timing for the use of rituximab in the disease course of SSc-ILD (eg, in patients with an initial diagnosis of SSc-ILD vs. in stable SSc-ILD vs. progressive SSc-ILD)."

## *International Society of Heart and Lung Transplantation*

In 2010, the International Society of Heart and Lung Transplantation (ISHLT) published evidence-based consensus guidelines on the care of heart transplant recipients. These guidelines were updated in 2022. Per the updated guidelines, rituximab was recommended for:

- Desensitization therapy in human leukocyte antigen-sensitized heart transplant candidates (class 2b recommendation, usefulness/efficacy is less well-established; level C evidence, based on expert consensus);
- In combination treatments for antibody-mediated rejection (class 2a recommendation, weight of evidence/opinion favors usefulness/efficacy; level C evidence).
- Preoperatively if isohemagglutinin titers >1:32 or added post operatively in cases of increasing isohemagglutinin levels (class 2a recommendation, weight of evidence/opinion favors usefulness/efficacy; level C evidence)

The guidelines also stated that at this time, routine rituximab induction cannot be recommended in non-sensitized cardiac transplant recipients.

In 2018, the ISHLT published a consensus document on the management of antibodies in heart transplantation. Rituximab was suggested as a treatment option for sensitized patients awaiting heart transplantation.

## *National Institute for Health and Care Excellence*

### Multiple Sclerosis (MS)

The National Institute for Health and Care Excellence (2022) updated its guidance on the management of multiple sclerosis in primary and secondary care.[159] The guidance did not include rituximab.

### ANCA-Associated (Pauci-Immune) Glomerulonephritis

In 2014, the National Institute for Health and Care Excellence issued guidance rituximab in combination with glucocorticoids for treating antineutrophil cytoplasmic antibody-associated vasculitis.[16,4]

Rituximab, in combination with glucocorticoids, is recommended as an option for inducing remission in adults with anti-neutrophil cytoplasmic antibody [ANCA]-associated vasculitis (severely active granulomatosis with polyangiitis [Wegener's] and microscopic polyangiitis), only if:

> further cyclophosphamide treatment would exceed the maximum cumulative cyclophosphamide dose or cyclophosphamide is contraindicated or not tolerated or the

person has not completed their family and treatment with cyclophosphamide may materially affect their fertility or the disease has remained active or progressed despite a course of cyclophosphamide lasting 3–6months or the person has had uroepithelial malignancy.

The guidance did not offer conclusions on maintenance therapy.

## British Committee for Standards in Haematology

### Thrombotic Thrombocytopenic Purpura

The British Committee for Standards in Haematology (BCSH) published evidence-based consensus guidelines for treatment of TTP and thrombotic microangiopathy in 2012.[6] All recommendations were based on moderate quality (level B) evidence (based on randomized trials with important limitations or strong evidence from observational studies), but strength of recommendations was strong (level 1, confidence that benefits do or do not outweigh harms). Recommendations include:

## Table 2. BCSH Recommendations on Treatment of Thrombotic Thrombocytopenic Purpura

| Recommendations | LOE | SOR |
|---|---|---|
| In acute idiopathic TTP with neurological or cardiac pathology, which are associated with a high mortality, rituximab should be considered on admission, in conjunction with plasma exchange and corticosteroids<br>Ideally plasma exchange should be withheld for at least 4 hours after completing a rituximab infusion | 1B | Strong |
| Increased plasma exchange and/or rituximab therapy are the agents of choice in refractory or relapsing disease | 1B | Strong |
| In patients in remission who have a documented reduction of ADAMTS13 activity to <5%, elective therapy with rituximab can be considered | 1B | Strong |
| In resistant HIV-related TTP, rituximab could be considered | 2B | Weak |

LOE: level of evidence; SOR: strength of recommendation; TTP: thrombotic thrombocytopenic purpura.

## MS Coalition

In June 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS. Rituximab is listed among various options, involving

different mechanisms of action and modes of administration, which have shown benefits in patients with MS.

## American Academy of Neurology

### Multiple Sclerosis

The American Academy of Neurology (2018) updated its guidelines on disease-modifying therapies for adults with multiple sclerosis.[160] For patients with relapse-remitting multiple sclerosis, 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 rate 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 vs placebo (very low confidence in the evidence). For patients with progressive multiple sclerosis, 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 American Academy of Neurology recommended that clinicians counsel patients considering rituximab or other immunosuppressive agents regarding treatment risks (level B recommendation).

## National Multiple Sclerosis Society

The National Multiple Sclerosis Society does not include rituximab among its listed treatments for MS.[165]

## Neuromyelitis Optica Study Group

### Neuromyelitis Optica

The Neuromyelitis Optica Study Group (2014) published evidence-based consensus recommendations on the diagnosis and treatment of neuromyelitis optica.[102] Rituximab was recommended as first-line treatment, along with azathioprine, and as second-line treatment after azathioprine failure.

## International Society of Heart and Lung Transplantation

The International Society of Heart and Lung Transplantation (2010) published evidence-based consensus guidelines for the care of heart transplant recipients.[145] Rituximab was recommended for:

- Desensitization therapy in human leukocyte antigen–sensitized heart transplant candidates (class 2b recommendation, usefulness/efficacy is less well-established; level C evidence, based on expert consensus);
- In combination treatments for antibody-mediated rejection (class 2a recommendation, weight of evidence/opinion favors usefulness/efficacy; level C evidence)

In 2018, the International Society of Heart and Lung Transplantation published a consensus document on the management of antibodies in heart transplantation. Rituximab was suggested as a treatment option for sensitized patients awaiting heart transplantation.[162]

## International Society of Thrombosis and Haemostasis

In 2020, the International Society on Thrombosis and Haemostasis (ISTH) published guidelines for the treatment of thrombotic thrombocytopenic purpura (TTP). 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. 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."

Nephrotic syndrome

- "For children with frequently relapsing nephrotic syndrome who develop serious glucocorticoid-related adverse effects and for all children with steroid-dependent nephrotic syndrome, we recommend that glucocorticoid-sparing agents be prescribed, rather than no treatment or continuation with glucocorticoid treatment alone...Patients should ideally be in remission with glucocorticoids prior to the initiation of glucocorticoid sparing agents such as oral cyclophosphamide, levamisole, mycophenolate mofetil (MMF), rituximab, or calcineurin inhibitors (CNIs). Coadministration of glucocorticoids is recommended for ≥2 weeks following initiation of glucocorticoid-sparing treatment... Choosing the most appropriate glucocorticoid-sparing agent from among oral cyclophosphamide, levamisole, MMF, rituximab, and CNI is a decision that requires careful consideration of specific patient related issues such as resources, adherence, adverse effects, and patient preferences. Oral cyclophosphamide and levamisole may be preferable glucocorticoid-sparing therapies in frequently relapsing nephrotic syndrome. MMF, rituximab, CNIs, and to a lesser extent, oral cyclophosphamide may be preferable to glucocorticoid-sparing therapies in children with steroid-dependent nephrotic syndrome."

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. 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.

A KDIGO guideline for the management of ANCA-associated vasculitis (AAV) was published in March 2024. The following recommendations were provided:

- "We recommend that glucocorticoids in combination with rituximab or cyclophosphamide be used as initial treatment of new-onset AAV."
    - Rituximab was noted to be preferred over cyclophosphamide for induction therapy in AAV in the following populations: children and adolescents; premenopausal women and men concerned about fertility; frail older adults; those requiring glucocorticoid sparing; relapsing disease; and PR3-ANCA-associated disease.
- "We recommend maintenance therapy with either rituximab, or azathioprine and low-dose glucocorticoids after induction of remission."
    - Rituximab was noted to be preferred over azathioprine for maintenance therapy in AAV in the following populations: relapsing disease; PR3-ANCA-associated disease; frail older adults; those requiring glucocorticoid sparing; and azathioprine allergy.
- "Patients with relapsing disease should be reinduced, preferably with rituximab."
- "Refractory disease can be treated by an increase in glucocorticoids (intravenous or oral), by the addition of rituximab if cyclophosphamide induction had been used previously, or vice versa."

## Myasthenia Gravis Foundation of America

In 2020, a multinational Task Force appointed by the Myasthenia Gravis Foundation of America published updated recommendations for the management of myasthenia gravis. The following recommendations were made regarding the use of rituximab:

- "Rituximab should be considered as an early therapeutic option in patients with muscle-specific kinase antibody-positive (MuSK-Ab+) MG [myasthenia gravis] who have an unsatisfactory response to initial immunotherapy."

- "The efficacy of rituximab in refractory acetylcholine receptor-positive (AChR-Ab+) MG is uncertain. It is an option if patients fail or do not tolerate other immunosuppressive (IS) agents"

## Medicare National Coverage

There is no national coverage determination.

## Regulatory Status

In 1997, rituximab (Rituxan [Biogen; Genentech]) was initially approved by the US Food and Drug Administration (FDA) for the treatment of relapsed or refractory low-grade, CD20-positive, B-cell non-Hodgkin lymphoma (see **Related Policies**). Subsequent indications approved by FDA are summarized in **Table 3**.

In November 2018, Truxima (rituximab-abbs; Celltrion), July 2019 Ruxience (rituximab-pvvr; Pfizer), and December 2020 Riabni (rituximab-arrx; Amgen) were approved by the FDA as biosimilars of rituximab.

## Table 3. FDA-Approved Indications for Rituximab

| Date | Indication |
|---|---|
| 1997 | • Relapsed or refractory low-grade or follicular, CD20-positive, B-cell NHL [modified in 2008 to state, "as a single agent"] |
| 2006 | • First-line treatment of [modified in 2008 to state, "Previously untreated"] diffuse large B-cell, CD20-positive, NHL in combination with CHOP or other anthracycline-based chemotherapy regimens<br>• In combination with MTX to reduce signs and symptoms in adults with moderately to severely active RA who have had an inadequate response to 1 or more TNF-antagonist therapies<br>• First-line treatment of [modified in 2008 to state, "Previously untreated"] follicular, CD20-positive, B-cell NHL in combination with CVP chemotherapy [modified in 2011 to state, "in combination with first-line chemotherapy]<br>• Treatment of low-grade, CD20-positive, B-cell NHL in patients with stable disease or who achieve a PR or CR following first-line treatment with CVP chemotherapy [modified in 2008 to state, "Treatment of non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent, after first-line CVP chemotherapy"] |
| 2010 | • In combination with FC for the treatment of patients with previously untreated and previously treated CD20-positive CLL |
| 2011 | • Single-agent maintenance therapy for patients with follicular, CD20-positive, B-cell NHL who achieve a CR or PR to first-line rituximab in combination with chemotherapy |

| Date | Indication |
|---|---|
| | • In combination with glucocorticoids for the treatment of adult patients with Wegener granulomatosis and microscopic polyangiitis |
| 2018 | • Treatment of adult patients with moderate to severe pemphigus vulgaris |
| 2019 | • In combination with glucocorticoids for the treatment of adult and pediatric patients 2 years of age and older with patients with Wegener's granulomatosis and microscopic polyangiitis |

CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; CLL: chronic lymphocytic leukemia; CR: complete response; CVP: cyclophosphamide, vincristine, prednisone; FC: fludarabine, cyclophosphamide; FDA: Food and Drug Administration; MTX: methotrexate; NHL: non-Hodgkin lymphoma; PR: partial response; RA: rheumatoid arthritis; TNF: tumor necrosis factor.

## 2020 Update

Added Ruxience (rituximab-pvvr) to site-of-service review. Updated coverage criteria for the rituximab products for the treatment of rheumatoid arthritis by adding Rinvoq (upadacitinib) as a first-line treatment option. Updated information on pregnancy as document within the prescribing information and the guidelines from The American Society of Hematology (2019) for the treatment of immune thrombocytopenia (ITP).

## 2021 Update

Added the biosimilar Riabni (rituximab-arrx) to policy as a second-line agent for the treatment of all covered indications listed in policy. Added links to the ACR, EULAR/ACR, and SLICC criteria. Updated Practice Guidelines and Position Statements and References in policy.

## 2023 Update

Reviewed prescribing information of all drugs in the policy. Moved Ruxience to second line (non-preferred) products. Changed patient to individual throughout the policy for the process of standardization. Removed trademarks from the brand products throughout the policy for the process of standardization. Added preferred Humira biosimilars (Amjevita with NDC starting with 55513, Cyltezo LCF, Hyrimoz HCF and adamilumab- adaz HCF (Sandoz – unbranded) to the list of preferred products to be tried and failed prior to using preferred Rituxan products as second line therapy for the indication of Rheumatoid Arthritis. Updated Amjevita [NDCs starting with 55513] to a non-preferred product effective January 1, 2024. Added Hyrimoz (Cordavis) [NDCs starting with 83457] as a non-preferred product effective January 1, 2024. Added adalimumab-adbm (Cyltezo unbranded) as a preferred product effective January 1, 2024.

Updated Hyrimoz LCF (Sandoz) from a non-preferred to a preferred product effective January 1, 2024.

## 2024 Update

Reviewed prescribing information of all drugs in the policy. Clarified that Humira (adalimumab) (AbbVie) [NDCs starting with 00074] is the preferred Humira product for rheumatoid arthritis. Added Simlandi (adalimumab-ryvk) and adalimumab-ryvk (Simlandi unbranded) as preferred products. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Added the following note to the rheumatoid arthritis criteria regarding the preferred adalimumab product list: This list of preferred adalimumab products does not apply to one Open formulary (Formulary ID: 6062; Rx Plan F1) and one Incentive formulary (Formulary ID: 6064; Rx Plan G3). The preferred adalimumab products for members with these custom Open and Incentive formulary plans are the following: Adalimumab-adaz (Hyrimoz unbranded), adalimumab-adbm (Cyltezo unbranded), adalimumab-ryvk (Simlandi unbranded), Cyltezo (adalimumab-adbm), Humira (adalimumab) (AbbVie) [NDCs starting with 00074], and Simlandi (adalimumab-ryvk). More details can be found in policy 5.01.647 Medical Necessity Criteria for Custom Incentive and Open Formularies. Please check the member Plan booklet or member ID card to determine whether this list of preferred adalimumab products applies. The following changes are effective January 3, 2025. Updated Hyrimoz (Sandoz) (adalimumab-adaz) [NDCs starting with 61314] from a preferred product to a non-preferred product. Changed Ruxience (rituximab-pvvr) to a preferred product. Changed Rituxan (rituximab) and Rituxan Hycela (rituximab and hyaluronidase human) to non-preferred products. Updated coverage criteria for Riabni (rituximab-arrx), Rituxan, and Rituxan Hycela to require the individual has had an adequate trial and failure with Ruxience or Truxima.

## 2025 Update

Policy updated to indicate that Site of Service Medical Necessity criteria does not apply to Alaska fully-insured members pursuant to **Alaska HB 226** (accessed January 3, 2025). Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added an exception to the site-of-service requirements for certain individuals receiving treatment for cytokine release syndrome (CRS). Removed Humira

(adalimumab) (AbbVie) [NDCs starting with 00074] as a first-line step therapy option for the rheumatoid arthritis criteria.

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## History

| Date | Comments |
|---|---|
| 01/13/15 | New policy, created with literature review through May 5, 2014. Add to Pharmacy section. Policy outlines the non-oncologic labeled and off-label indications for which Rituximab is considered medically necessary. |
| 07/15/15 | Minor edit. Removed link to policy 5.01.550. |
| 07/01/16 | Annual review, approved June 14, 2016. Medical necessity review criteria for site of service IV therapy added. Policy reformatted and reorganized. |
| 08/01/16 | Operational clarification. Clarified that medical necessity reviews for cancer diagnoses use policy 2.03.502. |
| 11/01/16 | Interim review, approved October 11, 2016. Clarified age criteria language indicating that site of service review is applicable to only those age 13 and older; drug criteria review applies to all ages. |
| 04/21/17 | Minor edit. Introduction section revised for clarity. |
| 07/01/17 | Formatting edit; added hyperlink menu for Medical Necessity Criteria sections. |
| 12/01/17 | Annual Review, approved November 14, 2017. Policy updated with literature review through August 24, 2017; references 10, 26, 60, 75, 82, 98-102, 135-136, and 145 added. “Antineutrophil cytoplasmic antibody–associated vasculitides” added to second medically necessary statement for clarification. Indication for use in patients with pemphigus changed to coverage at initial diagnosis. Note added regarding subsequent doses using Rituxan Hycela. Divided sections by covered versus investigational. Removed codes J3490 and J3590. |
| 02/14/18 | Interim Review, approved February 13, 2018. Update hospital based outpatient coverage from 30 days to 90 days. |

| Date | Comments |
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| 11/01/18 | Minor update, the Site of Service criteria was updated for clarity. |
| 01/01/19 | Annual Review, approved December 13, 2018. Policy updated with literature review through August 2018; references 23, 136-137, and 151-160 added; references 28 and 45 updated. Idiopathic membranous nephropathy was added to medical necessary statement. Added new HCPCS codes J9311 and J9312 (new codes effective 1/1/19). |
| 04/01/19 | Minor update, added Documentation Requirements section. |
| 08/01/19 | Interim Review, approved July 25, 2019. Added criteria for Truxima (rituximab-abbs) which is a biosimilar of Rituxan (rituximab). Added HCPCS code Q5115 to support Truxima. Title changed from "Rituxan (rituximab): Non-oncologic and Miscellaneous Uses" to "Rituximab: Non-oncologic and Miscellaneous Uses". |
| 12/01/19 | Annual Review, approved November 21, 2019. Policy updated with literature review through August 2019, references added. Policy statements unchanged |
| 01/01/20 | Interim Review, approved December 17, 2019, effective for dates of service on or after April 3, 2020, following provider notification. Rituxan (rituximab) and Ruxience (rixutimab-pvvr) noted as first-line products and Truxima (rituximab-abbs) as second line product. Added J3590 for Ruxience. Removed HCPCS code J9310 as it terminated 1/1/19. |
| 07/01/20 | Annual Review, approved June 18, 2020. Added Ruxience (rituximab-pvvr) to site-of-service review. Updated coverage criteria for the rituximab products for the treatment of rheumatoid arthritis by adding Rinvoq (upadacitinib) as a first-line treatment option. Changes to Ruxience for site of service review are effective for dates of service on or after October 2, 2020, following 90-day provider notification. Added code Q5119 for Ruxience, removed unlisted code J3590. |
| 10/01/20 | Interim Review, approved September 8, 2020. Updated coverage criteria for Rituxan (rituximab) and Ruxience (rituximab-pvvr) for the treatment of NMOSD requiring documentation of diagnosis of NMOSD and removing requirement to use an immunosuppressive drug prior to a rituximab product. |
| 02/01/21 | Annual Review, approved January 6, 2021. Added the biosimilar Riabni (rituximab-arrx) as a second line product. Added HCPCS code J3590. |
| 07/01/21 | Coding update, Added HCPCS code Q5123 and removed HCPCS code J3590. |
| 07/01/22 | Interim Review, approved June 14, 2022. Moved Truxima (rituximab-abbs) to being a preferred rituximab product. Updated coverage criteria for the non-preferred product Riabni (rituximab-arrx) to require the patient has had an adequate trial and failure with Rituxan, Ruxience, or Truxima. For the autoimmune hemolytic anemias updated coverage criteria from cold agglutination syndrome to cold agglutinin disease. Deleted effective date for HCPC code Q5123. |
| 09/01/23 | Annual Review, approved August 8, 2023. Changed the wording from "patient" to "individual" throughout the policy for standardization. Reviewed prescribing information of all drugs in the policy. Added preferred Humira biosimilars (Amjevita with NDC starting with 55513, Cyltezo LCF, Hyrimoz HCF and adamilumab- adaz HCF (Sandoz – unbranded) to the list of preferred products to be tried and failed prior to using preferred Rituxan products as second line therapy for the indication of Rheumatoid Arthritis. Effective January 1, 2024, following a 90 day provider |

| Date | Comments |
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| | notification, following changes were made: Moved Ruxience to second line (non-preferred) agent, . Added HCPCS code J3590. |
| 01/01/24 | Interim Review, approved December 26, 2023. Updated preferred adalimumab products within the preferred rituximab product criteria to Humira (adalimumab), Cyltezo (adalimumab-adbm), Hyrimoz (adalimumab-adaz) (Sandoz) [NDCs starting with 61314], adalimumab-adaz (Hyrimoz unbranded) and adalimumab-adbm (Cyltezo unbranded). |
| 05/01/24 | Annual Review, approved April 9, 2024. Clarified that Humira (adalimumab) (AbbVie) [NDCs starting with 00074] is the preferred Humira product for rheumatoid arthritis. |
| 07/01/24 | Interim Review, approved June 11, 2024. Added Simlandi (adalimumab-ryvk) and adalimumab-ryvk (Simlandi unbranded) as preferred products. Added Simlandi to HCPCS code J3590. |
| 10/01/24 | Interim Review, approved September 10, 2024. The following policy changes are effective January 3, 2025, following a 90-day provider notification. Changed Ruxience (rituximab-pvvr) to a preferred product. Changed Rituxan (rituximab) and Rituxan Hycela (rituximab and hyaluronidase human) to non-preferred products. Updated coverage criteria for Riabni (rituximab-arrx), Rituxan, and Rituxan Hycela to require the individual has had an adequate trial and failure with Ruxience or Truxima. Updated Hyrimoz (Sandoz) (adalimumab-adaz) [NDCs starting with 61314] from a preferred product to a non-preferred product. |
| 01/01/25 | Interim Review, approved December 23, 2024. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Added the following note to the rheumatoid arthritis criteria regarding the preferred adalimumab product list: This list of preferred adalimumab products does not apply to one Open formulary (Formulary ID: 6062; Rx Plan F1) and one Incentive formulary (Formulary ID: 6064; Rx Plan G3). The preferred adalimumab products for members with these custom Open and Incentive formulary plans are the following: Adalimumab-adaz (Hyrimoz unbranded), adalimumab-adbm (Cyltezo unbranded), adalimumab-ryvk (Simlandi unbranded), Cyltezo (adalimumab-adbm), Humira (adalimumab) (AbbVie) [NDCs starting with 00074], and Simlandi (adalimumab-ryvk). More details can be found in policy 5.01.647 Medical Necessity Criteria for Custom Incentive and Open Formularies. Please check the member Plan booklet or member ID card to determine whether this list of preferred adalimumab products applies. |
| 02/01/25 | Annual Review, approved January 27, 2025. Policy updated to indicate that Site of Service Medical Necessity criteria does not apply to Alaska fully-insured members; only Medical Necessity criteria for the infusion drug applies pursuant to Alaska HB 226 (link added). Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added an exception to the site- |

| Date | Comments |
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| | of-service requirements for certain individuals receiving treatment for cytokine release syndrome (CRS). |
| 03/01/25 | Interim Review, approved February 11, 2025. The following policy changes are effective July 1, 2025, following a 90-day provider notification. Removed Humira (adalimumab) (AbbVie) [NDCs starting with 00074] as a first-line step therapy option for the rheumatoid arthritis criteria. |



**Scope**: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.