Rituxan® (rituximab): Non-oncologic and Miscellaneous Uses

Introduction

Rituxan® (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 rituximab 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.
Note: This policy does not apply if the member has a cancer diagnosis (for these cases see policy 2.03.502 Monoclonal Antibodies for the Treatment of B-Cell Malignancies).

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

For those age 13 and 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:**

- **Rituxan®** (rituximab)

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

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<th>Neuromyelitis Optica (NMO)</th>
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<td>Pemphigoid Diseases</td>
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<td>Churg-Strauss Syndrome</td>
<td>Pemphigus Diseases</td>
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<tr>
<td>Cryoglobulinemic Vasculitis Associated with Hepatitis-C Virus (HCV)</td>
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<td>Microscopic Polyangiitis</td>
<td>Thrombotic Thrombocytopenic Purpura (TTP)</td>
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<td>Multicentric Castleman Disease</td>
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<td>Site of Service Administration</td>
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<tr>
<td><strong>Medically necessary sites of service</strong></td>
<td>IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost effective site:</td>
</tr>
<tr>
<td>• Physician’s office</td>
<td>• These are the preferred <strong>medically necessary</strong> sites of service for specified drugs.</td>
</tr>
<tr>
<td>• Infusion center</td>
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<tr>
<td>• Home infusion</td>
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<tr>
<td><strong>Hospital-based outpatient setting</strong></td>
<td>IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site.</td>
</tr>
<tr>
<td>• Outpatient hospital IV infusion department</td>
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<tr>
<td>• Hospital-based outpatient clinical level of care</td>
<td><strong>This site is considered medically necessary for the first 90 days for the following:</strong></td>
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<tr>
<td></td>
<td>• The initial course of infusion of a pharmacologic or biologic agent <strong>OR</strong></td>
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<tr>
<td></td>
<td>• Re-initiation of an agent after 6 months or longer of non-use with a known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug</td>
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<tr>
<td></td>
<td><strong>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.</strong></td>
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<tr>
<td></td>
<td><strong>This site is considered medically necessary only when the patient has a clinical condition which puts him or her at increased risk of complications for infusions, including any ONE of the following:</strong></td>
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<tr>
<td></td>
<td>• Known cardiac condition (eg, symptomatic cardiac arrhythmia) or pulmonary condition (eg, significant respiratory disease, serious obstructive airway disease, %FVC ≤ 40%) that may increase the risk of an adverse reaction</td>
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<td></td>
<td>• Unstable renal function which decreases the ability to respond to fluids</td>
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<td></td>
<td>• Difficult or unstable vascular access</td>
</tr>
<tr>
<td></td>
<td>• Acute mental status changes or cognitive conditions that</td>
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</table>
Site of Service Administration | Medical Necessity
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impact the safety of infusion therapy
- A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug.

Hospital-based outpatient setting
- Outpatient hospital IV infusion department
- 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
--- | ---
Rituxan® (rituximab) is subject to review for site of service administration. After the initial infusion of Rituxan®, subsequent doses using Rituxan Hycela™ may be used.

Arthropathies

Rheumatoid Arthritis (RA)
- See also: Related Policy 5.01.550 Pharmacotherapy of Arthropathies

Rituxan® (rituximab) may be considered medically necessary when:
- Treating of moderately to severely active rheumatoid arthritis (eg, ≥8 swollen and ≥8 tender joints)
- Administered in combination with methotrexate

AND
- Rituxan® (rituximab) is used as a second-line therapy when either:
  - The patient has tried and failed any one of the first line therapies listed below:
    1. Humira® (adalimumab)
    OR
    2. Enbrel® (etanercept)
    OR
    3. Remicade® (infliximab)
    OR
    4. Actemra® (tocilizamab)
    OR
    5. Xeljanz® (tofacitinib)/ Xeljanz XR® (tofacitinib extended release)
**Condition** | **Medical Necessity**
---|---
Rituxan® (rituximab) is subject to review for site of service administration. After the initial infusion of Rituxan®, subsequent doses using Rituxan Hycela™ may be used. | **OR**  
- The patient has had an adequate response to methotrexate or other conventional synthetic disease-modifying anti-rheumatic drug (DMARD)  
**AND**  
- The patient is not a suitable candidate for treatment with TNF inhibitors (eg, due to a recent [ie, within 5 years] history of lymphoma or other malignancy; latent tuberculosis, and contraindication to chemoprophylaxis; or previous demyelinating disease. |

### Miscellaneous Autoimmune Diseases

**Antineutrophil Cytoplasmic Antibody – Associated vasculitides:**
- Wegener’s Granulomatosis  
- (Granulomatosis with polyangiitis)  
- Microscopic Polyangiitis

**Rituxan® (rituximab) may be considered medically necessary when:**
- Initial therapy with azathioprine, methotrexate and/or mycophenolate has been tried and failed or is contraindicated.  
- Rituximab is used in combination with glucocorticoids.

**Neuromyelitis Optica (NMO)**

**Rituxan® (rituximab) may be considered medically necessary when:**
- The patient is refractory to at least one standard immunosuppressive drug (eg, azathioprine or mycophenolate mofetil).

**Cryoglobulinemic Vasculitis associated with Hepatitis-C Virus (HCV)**

**Rituxan® (rituximab) may be considered medically necessary when:**
- Rituximab is used as add-on therapy for patients who have:  
  - Active disease resistant to anti-viral drugs  
  **OR**  
  - Severe or life-threatening cryoglobulinemic vasculitis

**Systemic Lupus Erythematosus (SLE)**

**Rituxan® (rituximab) may be considered medically necessary when:**
- Rituximab is used as add-on therapy for patients with the following:
Rituxan® (rituximab) is subject to review for site of service administration. After the initial infusion of Rituxan®, subsequent doses using Rituxan Hycela™ may be used.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus Nephritis</td>
<td><strong>Rituxan® (rituximab) may be considered medically necessary when:</strong></td>
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<tr>
<td></td>
<td>• Rituximab is used as add-on therapy in patients who are refractory to at least</td>
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<tr>
<td></td>
<td>two standard first-line treatment regimens, and initial treatment has been</td>
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<tr>
<td></td>
<td>with any two of the following:</td>
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<tr>
<td></td>
<td>o Cyclophosphamide, azathioprine, or other immunosuppressant</td>
</tr>
<tr>
<td></td>
<td>o Corticosteroid (in addition to the above)</td>
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<tr>
<td>Primary Sjögren Syndrome</td>
<td><strong>Rituxan® (rituximab) may be considered medically necessary when:</strong></td>
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<tr>
<td></td>
<td>• Rituximab is used for patients refractory to corticosteroids and other</td>
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<tr>
<td></td>
<td>immunosuppressive agents (hydroxychloroquine and/or methotrexate), then any</td>
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<tr>
<td></td>
<td>one of the following:</td>
</tr>
<tr>
<td></td>
<td>o Cyclophosphamide or</td>
</tr>
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<td></td>
<td>o Mycophenolate or</td>
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<tr>
<td></td>
<td>o Azathioprine</td>
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<tr>
<td>Systemic Sclerosis (scleroderma)</td>
<td><strong>Rituxan® (rituximab) may be considered medically necessary when:</strong></td>
</tr>
<tr>
<td></td>
<td>• Rituximab is used for patients refractory to first-line treatment with</td>
</tr>
<tr>
<td></td>
<td>cyclophosphamide or glucocorticoids.</td>
</tr>
<tr>
<td>Churg-Strauss Syndrome (eosinophilic granulomatosis with polyangiitis)</td>
<td><strong>Rituxan® (rituximab) may be considered medically necessary when:</strong></td>
</tr>
<tr>
<td></td>
<td>• Rituximab is used as first-line treatment in combination with corticosteroids</td>
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<tr>
<td></td>
<td>for patients with severe (organ-threatening) disease.</td>
</tr>
</tbody>
</table>
**Condition** | **Medical Necessity**
--- | ---
Rituxan® (rituximab) is subject to review for site of service administration. After the initial infusion of Rituxan®, subsequent doses using Rituxan Hycela™ may be used. | OR
| • Rituximab is used as add-on therapy for treatment-refractory disease.

**Autoimmune Dermatologic Diseases**

<table>
<thead>
<tr>
<th>Pemphigoid Diseases:</th>
<th>Rituxan® (rituximab) may be considered medically necessary when to treat refractory patients with pemphigoid diagnoses when:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bullous pemphigoid</td>
<td>• Standard initial treatment was tried and failed. Standard initial treatment includes at least two of the following:</td>
</tr>
<tr>
<td>• Mucous membrane pemphigoid (including ocular cicatricial pemphigoid)</td>
<td>o Glucocorticoids, azathioprine, mycophenolate, or dapsone</td>
</tr>
<tr>
<td>• Epidermolysis bullosa acquisita</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Pemphigus Diseases:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pemphigus vulgaris</td>
<td></td>
</tr>
<tr>
<td>• Pemphigus foliaceus</td>
<td></td>
</tr>
<tr>
<td>• Paraneoplastic pemphigus</td>
<td></td>
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</tbody>
</table>

**Hematologic**

<table>
<thead>
<tr>
<th>Autoimmune hemolytic anemias (AIHA)</th>
<th>Rituxan® (rituximab) may be considered medically necessary when:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Warm AHIA</td>
<td>• Rituximab is used to treat warm AIHA in corticosteroid-refractory or corticosteroid–dependent patients</td>
</tr>
<tr>
<td>• Cold AHIA</td>
<td>AND</td>
</tr>
<tr>
<td></td>
<td>• Rituximab is used to treat cold agglutination syndrome.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Idiopathic (immune) Thrombocytopenic Purpura</th>
<th>Rituxan® (rituximab) may be considered medically necessary second line therapy when:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• In patients whose platelet counts continue to be at or less than 30,000 after first-line treatment using any one of the following:</td>
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<tr>
<td></td>
<td>o IVIg</td>
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<tr>
<td></td>
<td>OR</td>
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<td></td>
<td>o High-dose corticosteroids</td>
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<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>o Anti-D immunoglobulin</td>
</tr>
</tbody>
</table>

| Thrombotic | Rituxan® (rituximab) may be considered medically necessary |
Rituxan® (rituximab) is subject to review for site of service administration. After the initial infusion of Rituxan®, subsequent doses using Rituxan Hycela™ may be used.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| **Thrombocytopenic Purpura (TTP)**                  | *when:*  
|                                                     | • Rituximab is used in patients with refractory disease or relapse (ie, lack of response to plasma exchange therapy and corticosteroids). |
| **Chronic Graft-Versus-Host Disease**               | Rituxan® (rituximab) may be considered medically necessary when:  
|                                                     | • Rituximab is used in patients refractory to corticosteroids, who have chronic GVHD. |
| **Desensitization of human Leukocyte Antigen (HLA)**| Rituxan® (rituximab) may be considered medically necessary when:  
|                                                     | • Rituximab is to be used in HLA-sensitized renal transplant candidates before transplantation. |
| **Hemophilia**                                      | Rituxan® (rituximab) may be considered medically necessary when:  
|                                                     | • Rituximab is used as a factor inhibitor for patients who are refractory to conventional first-line treatments (eg, immune tolerance induction, corticosteroids with or without cyclophosphamide).  
|                                                     | **AND**  
|                                                     | • Rituximab is used as an add-on therapy |
| **Other**                                           | Rituxan® (rituximab) may be considered medically necessary when:  
|                                                     | • Rituximab is used in patients with or without chemotherapy. |
| **Multicentric Castleman Disease**                  | Rituxan® (rituximab) is investigational for all other non-oncologic uses, including but not limited to:  
| (angiofollicular lymph node hyperplasia)            | • paroxysmal cold hemoglobinuria  
|                                                     | • mixed connective tissue disease  
|                                                     | • multiple sclerosis  
|                                                     | • prophylaxis for graft-versus-host disease |
Drug Investigational

- induction immunosuppressive therapy for kidney transplantation
- treatment of antibody-mediated rejection in solid organ transplant recipients
- treatment of antibody-mediated rejection after pancreatic islet transplantation
- treatment of myasthenia gravis
treatment of minimal change disease

All other uses of Rituxan® (rituximab) for conditions not outlined in this policy are considered investigational.

### Dosage and Quantity Limits

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage and Quantity Limit of Rituxan® (rituximab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>• In combination with methotrexate, dosing is two 100 mg IV infusions, separated by 2 weeks (one course) every 24 weeks or based on clinical evaluation but no sooner than every 16 weeks.</td>
</tr>
<tr>
<td>Wegener’s granulomatosis (granulomatosis with polyangiitis)</td>
<td>• In combination with glucocorticoids, dosing is 375 mg / m² once weekly for 4 weeks.</td>
</tr>
<tr>
<td>For all other indications</td>
<td>• There is no dosing information provided in the package insert.</td>
</tr>
</tbody>
</table>

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCPCS</td>
<td></td>
</tr>
<tr>
<td>J9310</td>
<td>Injection, rituximab, 100 mcg (Rituxan®, generic rituximab)</td>
</tr>
</tbody>
</table>

### Related Information
Dosing

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

Adverse Events

Rituxan® (rituximab) carries the following black box warnings:

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

Labelled warnings and precautions include:

- Tumor lysis syndrome (for patients with hematologic malignancies)
- Infections
- Cardiac arrhythmias and angina
- Bowel obstruction and perforation
- Live virus vaccines: Do not administer live virus vaccines before or during rituximab therapy
- Cytopenias

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.
Pregnancy

Rituxan® (rituximab) is pregnancy category C: There are no adequate and well-controlled studies of rituximab in pregnant women. Women of childbearing potential should use effective contraception while receiving rituximab and for 12 months after treatment. Rituximab may be used during pregnancy only if potential benefit justifies potential risks to the 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) 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 administered by intravenous infusion.

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.
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. 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. 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. 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.

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.
Food and Drug Administration–Off-Label Covered Uses

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. Corticosteroids are first-line treatment in warm AIHA but less effective in cold AIHA.21,22

Evidence for rituximab in AIHA comprises a small number of patients with primary (idiopathic) and secondary disease. For warm AIHA, 2 RCTs found higher response rates with rituximab than with a control condition in patients with previously untreated disease. Serious adverse events were higher with rituximab than corticosteroids (1 RCT) but lower than placebo (the other RCT). For cold agglutinin syndrome, which generally has a poorer response than warm AIHA to first-line corticosteroids, a response rate of 62% was reported. A meta-analysis including 21 studies estimated a pooled ORR at 79% in warm AIHA and 57% in cold agglutinin syndrome, but the potential for publication bias suggested these estimates biased upward. As a potential glucocorticoid-sparing agent in warm AIHA and effective treatment for cold agglutinin syndrome, rituximab may improve health outcomes. Rituximab is not considered a treatment option for paroxysmal cold hemoglobinuria and is a covered indication, and is a covered indication.

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

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.28,29

Rituximab is being studied as a splenectomy-delaying or -avoiding approach in patients with idiopathic thrombocytopenic purpura (ITP). Two systematic reviews of primarily observational
studies (1 in children [median age, 8 years], 1 in adults) and 2 RCTs in adults investigated mostly non-splenectomized patients. Overall and complete response rates were approximately 57% and 40%, respectively, in adults, and 68% and 39% in children. Median response durations were approximately 1 year. One RCT of newly diagnosed patients reported an improved overall response rate with rituximab in combination with corticosteroid compared with corticosteroid alone, but another did not. AE reporting was inconsistent; serious infections and hypersensitivity reactions occurred in 4% of 370 children included in the systematic review. Overall, evidence suggests potentially improved health outcomes in patients with steroid-refractory ITP who are able to delay or avoid splenectomy with rituximab treatment. This is a covered indication.

**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). 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. When ADAMTS13 is absent or depleted, large uncleaved von Willebrand factor multimers aggregate in high shear areas of the microvasculature, leading to thrombotic microangiopathy. The main treatment for TTP is plasma exchange (PE) and corticosteroids. Refractory TTP, defined as progression of clinical symptoms during PE therapy, occurs in 10% to 20% of acquired TTP cases. For these patients, increased PE and/or addition of cyclosporine are current treatment options.

Studies of rituximab in TTP enrolled patients with acquired (anti-ADAMTS13 antibody-positive) TTP. One small phase 2 cohort study in patients with new-onset or relapsed TTP showed no difference in comparison with historical controls in the number of plasma exchange (PE) treatments needed to achieve remission. For patients with relapsed or refractory TTP, observational studies (case reports and case series) reported remission in 98% of rituximab-treated patients with a median follow-up of 10 months. This evidence suggests that, despite a small (3%) risk of serious adverse events (SAEs) with rituximab, some patients treated with PE who have relapsed or refractory disease may benefit from the addition of rituximab. Because progressive disease is potentially life-threatening and because relapsed and refractory patients have few alternative treatment options, rituximab may be considered medically necessary in this setting. Approximately half of clinical reviewers who provided input when this policy was under review in 2014 supported the use of rituximab in TTP. This is a covered indication.
Churg-Strauss Syndrome

Churg-Strauss syndrome, also called eosinophilic granulomatosis with polyangiitis (EGPA), is an ANCA-associated vasculitis characterized by peripheral and tissue eosinophilia, frequently affecting the lungs, in patients with asthma. 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 GPA and MPA, rituximab has been used in patients with EGPA syndrome refractory to conventional immunosuppressant therapy.

Evidence for rituximab in Churg-Strauss syndrome comprises case reports and a case series in treatment-refractory patients, all of whom responded to rituximab add-on therapy. Treatment-related AEs—some severe—have been reported. Because little is known about treatment options for patients refractory to conventional immunosuppressants, and because rituximab has demonstrated efficacy in other antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]), rituximab may be considered medically necessary when used as add-on therapy in patients with treatment refractory Churg-Strauss syndrome. Clinical input received when this policy was under review in 2014 also supported the use of rituximab in combination with corticosteroids as first-line treatment for severe (eg, organ-threatening) disease. This is a covered indication.

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. If left untreated, antibody inhibitors eventually render replacement therapy ineffective. Immune tolerance induction (ITI) is recommended first-line treatment of factor inhibitors in hemophilia. 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 (eg, anaphylaxis, irreversible nephrotic syndrome) are significant. Other regimens incorporate immunosuppressive drugs. 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.47

Rituximab for factor inhibitor eradication in congenital hemophilia and acquired hemophilia A has been studied in a small number of patients, primarily in case reports and cohort studies. In immune tolerance induction (ITI)–refractory patients with congenital hemophilia and factor inhibitor, complete remission (CR) occurred in 53% of patients who received rituximab alone or in combination with continued ITI; a small cohort study supported combination therapy in the refractory setting. A comparative study in acquired hemophilia A did not find improved response rates in patients treated with rituximab alone or in combination compared with standard cyclophosphamide plus cyclosporine. Evidence does not support rituximab as an alternative to standard treatments for factor inhibitor eradication (ie, ITI in congenital hemophilia and immunosuppression with cyclophosphamide and corticosteroids in acquired hemophilia A). However, evidence suggests that patients who are refractory to these first-line treatments may benefit from rituximab without an increase in AEs. Combination regimens may be preferred. Given the lack of treatment options in refractory patients and the serious, possibly fatal, outcomes if factor inhibitors are not eradicated, rituximab may be considered medically necessary in this setting. This is a covered indication.

**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.51,52

Recent reviews summarized the literature for rituximab to treat hepatitis C virus (HCV)–associated cryoglobulinemic vasculitis. Across 2 RCTS and many observational studies (total N=377), median overall response was approximately 80%. However, these studies were done before the advent of several new HCV antiviral drugs and pegylated interferon–free drug regimens. More effective antiviral treatments should improve outcomes, eg, virologic and
immunologic responses and cure rate of both HCV and associated vasculitis. However, for patients with antiviral-resistant active disease or with severe or life-threatening cryoglobulinemic vasculitis, rituximab in combination with current treatments may improve health outcomes. Viral load and liver function tests should be monitored during rituximab treatment.

**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. 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. Other treatments include combination chemotherapy and tocilizumab, a monoclonal anti-interleukin 6 antibody. Evidence for rituximab in multicentric Castleman disease comes almost exclusively from the HIV literature, which reflects the epidemiology of the disease. Prospective and retrospective cohort studies reported reduced incidence of subsequent non-Hodgkin lymphoma and substantially improved overall survival (≥93% at 2 years in 2 studies; 90% at 5 years in 1 study) in rituximab-treated patients compared with non-rituximab-treated unmatched controls. Progression or emergence of Kaposi sarcoma is an associated risk of rituximab treatment, with Kaposi sarcoma recurrence in approximately 30% of patients. No studies comparing rituximab with currently suggested first-line treatment with ganciclovir or valganciclovir were identified. However, given the low-quality evidence supporting this recommendation and aggressive course of multicentric Castleman disease, effective treatment with rituximab may outweigh its associated risks. Therefore, rituximab may be considered medically necessary for multicentric Castleman disease in the first- or second-line setting.

**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, and treatments may differ. An autoantibody to aquaporin 4, a water channel found in high concentrations at the blood-brain barrier, is included in NMO diagnostic criteria. Curative treatment does not currently exist; treatment goals are: relapse remission, relapse prevention, and symptom relief. Immunosuppression with azathioprine or mycophenolate mofetil (MMF) is commonly used for relapse prevention. Rituximab is being studied for relapse prevention in NMO.

The evidence base for use of rituximab to prevent relapse in NMO is comprised of uncontrolled observational studies and systematic review. A 2016 systematic review of 46 uncontrolled studies found significant reductions in the relapse rate and EDSS score after beginning treatment with rituximab. In a retrospective review of 90 patients previously treated with MS treatments (eg, β-interferon, glatiramer acetate), the efficacy of rituximab appeared comparable with that of azathioprine and MMF, considered first-line immunosuppressive drugs for NMO. A retrospect-prospective cohort has suggested rituximab as, or possibly more, effective than other agents in preventing relapse. Based on adverse events reported, the safety of rituximab in NMO appeared comparable to the safety in other patient populations. This is a covered indication.

### Pemphigoid and Pemphigus Diseases

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.

Evidence for rituximab in pemphigoid diseases and pemphigus, refractory to first-line treatment is comprised of case reports, case series, retrospective cohort studies of patients with pemphigus, and a 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 adverse event 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.

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.

**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. Treatment focuses on symptom relief; corticosteroids, immunosuppressive drugs, or IVIG may be prescribed for severe complications.

Patients with primary Sjögren syndrome who require more than symptomatic treatment for severe glandular or extraglandular disease are generally treated with corticosteroids and immunosuppressive drugs. Rituximab has been studied in a small number of patients in randomized and nonrandomized trials and observational studies. Efficacy of rituximab was not consistently demonstrated, eg, a large (N=120) randomized trial showed no difference in response compared with placebo in mostly untreated patients, and a small (N=41) nonrandomized trial showed statistically significant differences in response compared with disease-modifying antirheumatic drugs (DMARDs) in previously treated patients. Incidence of AEs did not appear to be increased above that observed in other patient populations. Given the limited treatment options and potential serious outcomes, including death, for patients with refractory disease, rituximab may be considered medically necessary for these patients. Well-designed randomized trials comparing rituximab with alternative treatments for first-line and second-line therapy of primary Sjögren syndrome are needed. This is a covered indication.
**Systemic Lupus Erythematosus**

Evidence for rituximab in patients with refractory systemic lupus erythematosus (SLE) comprises 1 large RCT that did not show improved response rates at 1 year with rituximab add-on therapy; however, a stringent end point may have obscured clinically important treatment effects. Systematic reviews that included mostly cohort studies and case series of refractory patients generally reported higher response rates (25%-91% overall responses) than controlled studies. Rates of SAEs and severe AEs, mostly infections and infusion or allergic reactions, were 7% to 13%. This evidence suggests that for some SLE patients refractory to first-line treatments, add-on rituximab may improve health outcomes. This is a covered indication.

**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. 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%; 5% to 10% of LN patients will progress to end-stage renal disease at 10 years. Current treatment regimens include cyclophosphamide or MMF, both administered with corticosteroids. Response rates at 1 year are 50% to 80%, but they are often only partial responses.

Evidence for rituximab in refractory lupus nephritis (LN) includes 1 RCT that did not show improved overall response rates at 1 year with rituximab add-on therapy; however, this trial may have been underpowered to show an improvement in partial responses (PRs). Summaries of noncomparative studies reported CR and PR rates of 30% to 40% and approximately 35%, respectively, in patients with mostly refractory disease. AEs occurred in approximately 20% of patients. For some patients with refractory LN, add-on rituximab may improve health outcomes. However, because SAEs were observed in these patients (severe infections, febrile neutropenia, posterior reversible leukoencephalopathy), the risk-benefit profile of rituximab is improved when used after failure of 2 standard treatment regimens.

**Systemic Sclerosis (Scleroderma)**

Evidence for rituximab in treatment-refractory systemic sclerosis comprised observational studies and 1 small, unblinded trial. Rituximab as add-on or monotherapy generally improved skin symptoms and pulmonary function tests; AEs, including sepsis deaths, occurred in 21% to 47% of patients. This evidence suggests that rituximab may improve health outcomes in some...
patients with treatment-refractory systemic sclerosis. Because second-line treatment options are limited and the consequences of progressive disease may be life-threatening, rituximab may be considered medically necessary for these patients. This is a covered indication.

**Graft-Versus-Host Disease**

Rituximab for treatment of steroid-refractory chronic graft-versus-host disease (GVHD) has been examined in cohort studies, which show response in most patients, with sustained response and steroid reduction or discontinuation in some. Treatment options for patients with steroid-refractory GVHD are limited, rituximab may be considered medically necessary in this setting. This is a covered indication- treatment of chronic GVHD that is steroid resistant.

Evidence for rituximab prophylaxis for GVHD comprises 2 small cohort studies, 1 of which included a contemporaneous control group. Although results suggested that rituximab may reduce the incidence of GVHD, replication in larger, controlled trials is needed. Due to the risk of severe AEs with rituximab, improved health outcomes in the prophylactic setting cannot be assumed. Prophylaxis for GVHD is not covered and is considered investigational.

**Pretransplant HLA Desensitization in Kidney Transplantation.**

Patients who are HLA-sensitized have broadly reactive alloantibodies (eg, due to previous pregnancy, transfusion of blood or blood products, or transplantation). HLA-sensitized patients are difficult to match for donor organs because of high risks of hyperacute rejection and graft loss with cross-matched organs (ie, 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.156

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.
Off-Label Non-Covered – Investigational Uses

Antibody-Mediated Rejection

Antibody-mediated injury to allografts comprises ABMR, ABMR without complement deposition, antibody-mediated endarteritis, and accelerated arteriosclerosis of allografts.\textsuperscript{161} Induction immunosuppressive regimens initiated before, at the time of, or immediately after transplantation, mute T-cell responses to antigen presentation reduces acute rejection.\textsuperscript{162} Induction regimens typically are combination high-dose immunosuppressive agents or anti-T-cell antibodies (eg, antithymocyte globulin) plus lower dose immunosuppressive agents.

Evidence for rituximab induction to prevent acute antibody-mediated rejection (ABMR) comprised a meta-analysis of 5 very low-quality trials and 1 RCT. Although the meta-analysis indicated reduced ABMR and improved graft survival compared with controls, trial quality was very low. The RCT demonstrated increased mortality in the rituximab group at 3-year follow-up. A second RCT found no beneficial effect on biopsy-proven rejection. Rituximab has not been shown to improve health outcomes when used for induction immunosuppression in kidney transplant recipients.

Small numbers of heart and kidney transplant recipients with ABMR have been treated with rituximab in comparative studies. Although observed improvements in outcomes suggest potential benefit with rituximab, data are retrospective or from small prospective studies. Dose-response studies and larger RCTs with longer follow-up and are needed to demonstrate improved health outcomes with rituximab treatment of ABMR. This is a non-covered indication.

Case reports of four patients suggest a possible role for the use of rituximab with other agents to treat ABMR after pancreatic islet transplantation. Dose-response studies and larger RCTs with longer follow-up and are needed to demonstrate improved health outcomes with rituximab treatment of ABMR.

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 (eg, 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.

Evidence for rituximab in the treatment of idiopathic membranous nephropathy includes multiple observational studies and an RCT. Rituximab may have moderate benefit in patients with idiopathic membranous nephropathy who have failed previous treatment with other immunosuppressive regimens or those with a moderate risk of progression who have not previously received immunosuppressive therapy. However, a longer RCT is needed to confirm the benefits of rituximab and to determine the optimal schedule, dose and long-term safety and efficacy. This is an investigational indication.

**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.

Evidence for rituximab in treatment-refractory myasthenia gravis is comprised of multiple small uncontrolled studies, a systematic review of uncontrolled studies, and a small controlled observational study. A systematic review of 47 small uncontrolled studies found a significant reduction in a myasthenia gravis symptom score after beginning rituximab treatment and a relatively low rate of adverse events. However, 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. Although there are no randomized studies, there is a nonrandomized comparative study and numerous series, summarized in a systematic review, reporting positive outcomes. This is a non-covered indication.

**Minimal Change Disease**

Evidence for rituximab in treatment of minimal change disease includes multiple observational studies in adults and 2 RCTs plus multiple observational studies in children. Rituximab may benefit in 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 effects from their medications, because the long-term efficacy and safety of rituximab in this group of patients remain unclear. This is a non-covered indication.

**Mixed Connective Tissue Disease**

Mixed connective tissue disease (MCTD) has various features of systemic lupus erythematosus (SLE), systemic sclerosis, polymyositis/dermatomyositis (PM/DM), and RA in the presence of increased anti-ribonucleoprotein (anti-RNP) antibodies. 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.

Data from 2 case series with 6 or fewer patients with MCTD; each is insufficient to determine the efficacy and safety of rituximab for the treatment of MCTD. In one of the series, 3 of 5 patients with MCTD achieved partial remission with rituximab; 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. This evidence is insufficient to show improved health outcomes.

**Multiple Sclerosis**

Two RCTs have evaluated rituximab in patients with MS. One RCT in patients with RRMS showed improvements in MRI and clinical outcomes at 24-week follow-up. However, methodologic limitations restrict the conclusions that can be based on these data. The second RCT, which was well-designed and was conducted in patients with PPMS, demonstrated no effect of rituximab on disease progression. A large registry study found a relatively low rate of adverse events and relapses and little change in disability scores; this study lacks a comparison group.

**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

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<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
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<th>Completion Date</th>
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<td>NCT01181154</td>
<td><strong>Rituximab in Adult’s Warm Auto-Immune Hemolytic Anemia</strong> : a Phase III, Double-bind, Randomised Placebo-controlled Trial</td>
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<td><strong>ANCA-associated vasculitis</strong></td>
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<td>NCT02433522</td>
<td>Comparison Between a Long Term and a Conventional Maintenance Treatment With Rituximab (MAINRITSAN3)</td>
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<td>NCT01697267</td>
<td><strong>Rituximab Vasculitis Maintenance Study</strong> (RITZAREM)</td>
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<td>NCT01808911</td>
<td>Outcome of Acquired Hemophilia With Steroid Combined With Cyclophosphamide Versus Steroid Combined With Rituximab (CREHA Study)</td>
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<td>Nov 2018</td>
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<td><strong>Pemphigoid and pemphigus diseases</strong></td>
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<td>NCT02383589a</td>
<td>A Study to Evaluate the Efficacy and Safety of Rituximab Versus Mycophenolate Mofetil (MMF) in Participants With Pemphigus Vulgaris (PV)</td>
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<td>NCT01748084</td>
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<td>NCT01862926</td>
<td>A Randomized, Double Blind Controlled Trial Comparing Rituximab Against Intravenous Cyclophosphamide in Connective Tissue Disease Associated Interstitial Lung Disease</td>
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<td>NCT01508468</td>
<td>Evaluate Rituximab Treatment for Idiopathic Membranous Nephropathy (GEMRITUX)</td>
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<td>NCT01180036</td>
<td>A Randomized Controlled Trial of Rituximab Versus Cyclosporine in the Treatment of Idiopathic Membranous Nephropathy (IMN)</td>
<td>126</td>
<td>Oct 2017 (ongoing)</td>
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### 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.

### 2014 Input

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 currently 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, IgM-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

Rheumatoid Arthritis

American College of Rheumatology

The American College of Rheumatology updated its evidence-based consensus guidelines on rheumatoid arthritis (RA) in 2015 and made the following recommendations:\textsuperscript{177}:

- If a patient has moderate (eg, Clinical Disease Activity Index [CDAI] >10-22 or Disease Activity Score in 28 joints [DAS-28] ≥3.2 to ≤5.1) or high (eg, 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.
National Institute for Health and Care Excellence

In 2010, the National Institute for Health and Care Excellence issued a guidance on adalimumab, etanercept, infliximab, rituximab, and abatacept for the treatment of RA after the failure of a TNF inhibitor.\textsuperscript{178} The recommendations involving rituximab include:

Rituximab in combination with methotrexate is recommended as treatment for patients with severe active rheumatoid arthritis who have had an inadequate response to, or are intolerant of other disease-modifying anti-rheumatic drugs (DMARDs), including at least one tumour necrosis factor (TNF) inhibitor. Treatment with rituximab should be given no more frequently than every 6 months.

Treatment with rituximab in combination with methotrexate should be continued only if there is an adequate response. An adequate response is defined as an improvement in disease activity score (DAS28) of 1.2 points or more.

European League Against Rheumatism

The European League Against Rheumatism’s (EULAR) 2013 recommendations for the management of RA with synthetic and biological DMARDs state, “In patients responding insufficiently to MTX and/or other conventional synthetic DMARD strategies, with or without glucocorticoids, biological DMARDs (TNF inhibitors, abatacept, or tocilizumab, and, under certain circumstances, rituximab) should be commenced with MTX.”\textsuperscript{132} The “certain circumstances” are: recent history of lymphoma; latent tuberculosis (TB) and contraindications to chemoprophylaxis; living in a TB-endemic area; or previous demyelinating disease.

International Consensus Expert Group

An international (mostly European) consensus group updated its evidence-based consensus statements in 2010\textsuperscript{133} and 2011\textsuperscript{134} The group supported consideration of rituximab when TNF inhibitors are not suitable (category D evidence) and in MTX-naive patients.
ANCA-Associated (Pauci-Immune) Glomerulonephritis

National Institute for Health and Care Excellence

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

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 3–6 months or the person has had uroepithelial malignancy.

The guidance did not offer conclusions on maintenance therapy.

Idiopathic Thrombocytopenic Purpura

American Society of Hematology

In 2011, American Society of Hematology published evidence-based guidelines for immune thrombocytopenia. Rituximab is suggested in the following clinical scenarios (all grade 2 suggestions based on level C evidence [RCTs with serious flaws, weaker observational studies, or indirect evidence]):

- Children or adolescents with ITP who have significant ongoing bleeding despite treatment with IVIG, anti-RhD immunoglobulin, or conventional doses of corticosteroids.

- Children and adolescents with chronic ITP as an alternative to splenectomy or in patients who do not respond favorably to splenectomy.

Adults with ITP who have failed 1 line of therapy, such as corticosteroid, IVIG, or splenectomy, and are at risk of bleeding. In 2015, the Society convened a panel of experts to review and revise the guidelines. Expected publication for its update is 2017.
**Thrombotic Thrombocytopenic Purpura**

**British Committee for Standards in Haematology**

The British Committee for Standards in Haematology (BCSH) published evidence-based consensus guidelines for treatment of TTP and thrombotic microangiopathy in 2012. 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:

**BCSH Recommendations on Treatment of Thrombotic Thrombocytopenic Purpura**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>1B</td>
<td>Strong</td>
</tr>
<tr>
<td>Ideally plasma exchange should be withheld for at least 4 hours after completing a rituximab infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased plasma exchange and/or rituximab therapy are the agents of choice in refractory or relapsing disease</td>
<td>1B</td>
<td>Strong</td>
</tr>
<tr>
<td>In patients in remission who have a documented reduction of ADAMTS13 activity to &lt;5%, elective therapy with rituximab can be considered</td>
<td>1B</td>
<td>Strong</td>
</tr>
<tr>
<td>In resistant HIV-related TTP, rituximab could be considered</td>
<td>2B</td>
<td>Weak</td>
</tr>
</tbody>
</table>

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

**Multicentric Castleman Disease**

**Centers for Disease Control and Prevention, National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America**

In 2013, the Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), and the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA) jointly published updated evidence-based guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. Rituximab is suggested as an
optional alternative therapy for multicentric Castleman disease; regimens with ganciclovir, valganciclovir are preferred. Guideline authors noted that patients who are treated with rituximab “may experience subsequent exacerbation or emergence of Kaposi sarcoma.” (Level C [optional] recommendation based on level 2 evidence [1 or more nonrandomized trials or observational studies with long-term clinical outcomes]).

**CDC, NIH, HIVMA/IDSA, Pediatric Infectious Diseases Society, and American Academy of Pediatrics**

In 2013, CDC, NIH, HIVMA/IDSA, Pediatric Infectious Diseases Society, and the American Academy of Pediatrics jointly published evidence-based guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children. Rituximab is not included among recommended treatments for multicentric Castleman disease.

**Multiple Sclerosis**

**American Academy of Neurology**

The American Academy of Neurology's guideline on disease-modifying therapies for MS has not been reaffirmed since 2008. It does not include rituximab.

**National Institute for Health and Care Excellence**

In April 2014, National Institute for Health and Care Excellence issued draft guidance for the management of MS in primary and secondary care. It does not include rituximab.

**National Multiple Sclerosis Society**

The National Multiple Sclerosis Society does not include rituximab among its listed treatments for MS.
Neuromyelitis Optica

Neuromyelitis Optica Study Group

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

Factor Inhibitors in Hemophilia

Congenital Hemophilia

UK Haemophilia Centre Doctors Organization

In 2013, UK Haemophilia Centre Doctors Organization updated its evidence-based consensus guideline for the diagnosis and treatment of factor VIII and factor IX inhibitors in congenital hemophilia. For patients undergoing ITI, rituximab is suggested as 1 of several strategies (along with FVIII dose increase; use of low-purity platelet-derived FVIII rather than recombinant FVIII; or discontinuation of ITI) if there is an inadequate decrease in inhibitor titer (≤20% reduction in 6 months). (Grade 2 [weak] recommendation based on level C [low quality] evidence.)

Acquired Hemophilia A

International Consensus Expert Group

In 2009, an international group of experts in the management of acquired hemophilia published evidence-based consensus recommendations on the diagnosis and treatment of patients with acquired hemophilia A. Rituximab alone or in combination with corticosteroids is suggested as second-line therapy if first-line inhibitor eradication therapy (with corticosteroids alone or in combination with cyclophosphamide) fails or is contraindicated. (Evidence grade not provided because all recommendations and suggestions were based on low quality evidence.)
Physicians World Europe

An expert panel, coordinated by Physicians World Europe, conducted a systematic review on the management of acquired hemophilia A and published their results in 2010.184 The panel recommended that patients receive immunosuppressive therapy immediately following diagnosis of acquired hemophilia A. If corticosteroid treatment does not induce remission, adding cyclophosphamide or rituximab is suggested, though rituximab is not currently approved for this indication.

Hepatitis C Virus–Associated Cryoglobulinemic Vasculitis

Kidney Diseases: Improving Global Outcomes

In 2012, KDIGO published evidence-based consensus guidelines for glomerulonephritis.10 Rituximab in combination with IV methylprednisolone and antiviral therapy is suggested as 1 of several treatment options (along with plasmapheresis or cyclophosphamide, also in combination with IV methylprednisolone and antiviral therapy) for patients with hepatitis C virus and mixed (IgG/IgM) cryoglobulinemia who have nephrotic proteinuria, progressive kidney disease, or an acute flare of cryoglobulinemia (Level 2 suggestion based on level D [very low quality] evidence).

Bullous Pemphigoid

British Association of Dermatologists

In 2012, the British Association of Dermatologists published evidence-based guidelines for the management of bullous pemphigoid.141 Rituximab received a level D recommendation based on level 3 evidence (case reports and case series).

Lupus Nephritis

American College of Rheumatology

In 2012, ACR published evidence-based consensus guidelines for the treatment of lupus nephritis.142 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
European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association

In 2012, EULAR and the European Renal Association–European Dialysis and Transplant Association published joint evidence-based consensus recommendations for the management of pediatric and adult lupus nephritis. For refractory disease, i.e., for patients not responding to cyclophosphamide (CYC) or mycophenolate mofetil (MMF), treatment may be switched from MMF to CYC or from CYC to MMF, or rituximab may be added or given as monotherapy (category 4 evidence, based on expert committee reports or opinions and/or clinical experience of respected authorities).

Kidney Diseases: Improving Global Outcomes

In 2012, KDIGO published evidence-based consensus guidelines for glomerulonephritis. Rituximab is suggested as 1 of several treatment options (along with IVIG and calcineurin inhibitors) for patients with lupus nephritis who have failed more than 1 first-line regimen (level 2 suggestion based on level D [very low quality] evidence).

Graft-Versus-Host Disease

British Committee for Standards in Haematology

In 2012, BCSH published evidence-based consensus guidelines for the diagnosis and management of acute GVHD and chronic GVHD.

Due to insufficient evidence (case reports), BSCSH does not recommend rituximab for acute GVHD.

- For chronic GVHD, BCSH makes 2 weak recommendations (the magnitude of benefit or not is less certain):
  - Rituximab is suggested as an option for second-line treatment of refractory cutaneous or musculoskeletal GVHD (Level B evidence, based on randomized trials with important limitations or strong evidence from observational studies).
Rituximab may be considered for third-line treatment of chronic GVHD involving other organs (Level C evidence, based on observational studies, case series or opinion).

**Consensus Conference on Clinical Practice in Chronic GVHD**

In 2011, Wolff et al published evidence-based consensus guidelines on second-line treatment of chronic GVHD. Rituximab was recommended as a reasonable second-line therapy of chronic GVHD, especially in patients with sclerodermatous, lichenoid cutaneous disease, and in autoantibody-mediated cytopenias (level C recommendation [evidence is insufficient to support for or against; use in greater than second-line treatment is justified] based on level II evidence [based on observational studies]). Evidence was insufficient to make dose recommendations.

**Solid Organ Transplant**

**International Society of Heart and Lung Transplantation**

In 2010, the International Society of Heart and Lung Transplantation published evidence-based consensus guidelines for the care of heart transplant recipients. 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)

**Kidney Diseases: Improving Global Outcomes**

In 2009, KDIGO published evidence-based consensus guidelines for the care of kidney transplant recipients. Rituximab is discussed but not included in any recommendations. For treatment of acute rejection, guideline authors noted that “the optimal protocol to treat acute humoral rejection remains to be determined,” and RCTs comparing safety and efficacy of various regimens are lacking. IVIG plus rituximab has been used to treat recurrent (post-transplant) hemolytic-uremic syndrome that is resistant to multiple courses of plasma exchange.
U.S. Preventive Services Task Force Recommendations

Rituximab for the treatment of various conditions is not a preventive service.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Regulatory Status

In 1997, rituximab (Rituxan® [Biogen, Cambridge MA; Genentech, South San Francisco, CA]) was initially approved by the U.S. Food and Drug Administration (FDA) for the treatment of relapsed or refractory low-grade, CD20-positive, B-cell non-Hodgkin lymphoma (see evidence review 2.03.05). Subsequent FDA-approved indications included rheumatoid arthritis in 2006 and granulomatosis with polyangiitis and microscopic polyangiitis in 2011, as shown in Table 2.

Table 2. FDA-Approved Indications of Rituximab by Date

<table>
<thead>
<tr>
<th>Date</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>• Relapsed or refractory low-grade or follicular, CD20-positive, B-cell NHL [modified in 2008 to state, “as a single agent”]</td>
</tr>
</tbody>
</table>
| 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  
       • 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  
       • 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”]  
       • 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  
       • In combination with glucocorticoids for the treatment of adult patients with Wegener granulomatosis and microscopic polyangiitis  |

References


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/13/15</td>
<td>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.</td>
</tr>
<tr>
<td>07/15/15</td>
<td>Minor edit. Removed link to policy 5.01.550.</td>
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<tr>
<td>07/01/16</td>
<td>Annual review, approved June 14, 2016. Medical necessity review criteria for site of service IV therapy added. Policy reformatted and reorganized.</td>
</tr>
<tr>
<td>08/01/16</td>
<td>Operational clarification. Clarified that medical necessity reviews for cancer diagnoses use policy 2.03.502.</td>
</tr>
<tr>
<td>11/01/16</td>
<td>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.</td>
</tr>
<tr>
<td>04/21/17</td>
<td>Minor edit. Introduction section revised for clarity.</td>
</tr>
<tr>
<td>07/01/17</td>
<td>Formatting edit; added hyperlink menu for Medical Necessity Criteria sections.</td>
</tr>
<tr>
<td>12/01/17</td>
<td>Annual Review, approved November 14, 2017. Policy updated with literature review</td>
</tr>
</tbody>
</table>

02/14/18  Interim Review, approved February 13, 2018. Update hospital based outpatient coverage from 30 days to 90 days.

11/01/18  Minor update, the Site of Service criteria was updated for clarity.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

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- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
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  - Qualified interpreters
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PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

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İlloko (Ilocano):
Kreyol ayisyen (Creole):
Avi silica a gen Enfòmasyon enpòtan ladinan. Avi silica a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsew konvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki epòtan nan avi silica a. Ou ka gen pou pran kék aksyon avan sèten dat limit pou ka knebe konvèti asirans sante w la oswa pou yo ka ede w avèk defans yo. Se dwa w pou resewa enfòmasyon sa a ak asisants nan lang ou paale a, san ou pa gen pou peye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

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Please call 800-722-1471 (TTY: 800-842-5357).

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세어 (Chinese):
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