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 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 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)

---

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

- Autoimmune hemolytic anemias (AIHA)
- Chronic Graft-Versus-Host Disease
- Churg-Strauss Syndrome
- Cryoglobulinemic Vasculitis Associated with Hepatitis-C Virus (HCV)
- Desensitization of Human Leukocyte Antigen (HLA)
- Hemophilia
- Idiopathic Membranous Nephropathy
- Idiopathic Thrombocytopenic Purpura
- Lupus Nephritis
- Microscopic Polyangiitis
- Multicentric Castleman Disease
- Neuromyelitis Optica (NMO)
- Pemphigoid Diseases
- Pemphigus Diseases
- Primary Sjögren Syndrome
- Rheumatoid Arthritis (RA)
- Site of Service
- Systemic Lupus Erythematosus (SLE)
- Systemic Sclerosis (scleroderma)
- Thrombotic Thrombocytopenic Purpura (TTP)
- Wegener’s Granulomatosis
<table>
<thead>
<tr>
<th>Site of Service Administration</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| **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:*
• These are the preferred **medically necessary** sites of service for specified drugs. |
| **Hospital-based outpatient setting**<br>• Outpatient hospital IV infusion department<br>• Hospital-based outpatient clinical level of care | *IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site.*

**This site is considered medically necessary for the first 90 days for the following:**
• The initial course of infusion of a pharmacologic or biologic agent
**OR**
• Re-initiation of an agent after 6 months or longer following discontinuation of therapy*

*Note: This does not include when standard dosing between infusions is 6 months or longer*

**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.**

**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:**
• Known cardiac condition (eg, symptomatic cardiac arrhythmia) or pulmonary condition (eg, significant respiratory disease,
### Site of Service Administration

<table>
<thead>
<tr>
<th><strong>Medical Necessity</strong></th>
</tr>
</thead>
</table>
| serious obstructive airway disease, %FVC ≤ 40%) that may increase the risk of an adverse reaction  
- Unstable renal function which decreases the ability to respond to fluids  
- Difficult or unstable vascular access  
- Acute mental status changes or cognitive conditions that 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

<table>
<thead>
<tr>
<th><strong>Medical Necessity</strong></th>
</tr>
</thead>
</table>
| **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 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:  
  o The patient has tried and failed any one of the first line therapies listed below:  
    1. Humira® (adalimumab) OR  
    2. Enbrel® (etanercept) OR |
**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.

3. Remicade® (infliximab)
OR
4. Actemra® (tocilizamab)
OR
5. Xeljanz® (tocafitinib) / Xeljanz XR® (tocafitinib extended release)

OR
- The patient has had an inadequate 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 (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.

### Miscellaneous Autoimmune Diseases

**Antineutrophil cytoplasmic antibody – associated (ANCA) vasculitides:**
- Wegener’s granulomatosis (granulomatosis with polyangiitis)
- Microscopic polyangiitis

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

**Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis)**

Rituxan® (rituximab) may be considered medically necessary for the treatment of Churg-Strauss syndrome when:
- Rituximab is used as first-line treatment in combination with glucocorticoids for patients with severe (organ-threatening) disease.

OR
- Rituximab is used as add-on therapy for treatment-refractory disease.

**Cryoglobulinemic vasculitis**

Rituxan® (rituximab) may be considered medically necessary
**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.

**associated with hepatitis-C virus (HCV)** | for the treatment of cryoglobulinemic vasculitis associated with hepatitis-C virus 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

**Idiopathic membranous nephropathy** | Rituxan® (rituximab) may be considered medically necessary for the treatment of idiopathic membranous nephropathy when:  
- Patients have failed prior treatment with other immunosuppressive regimens such as cyclophosphamide or chlorambucil plus glucocorticoids, or cyclosporine, or tacrolimus

**Lupus nephritis** | Rituxan® (rituximab) may be considered medically necessary for the treatment of lupus nephritis when:  
- Rituximab is used as add-on therapy in patients who are refractory to at least two standard first-line treatment regimens, and initial treatment has been with any two of the following:  
  - Cyclophosphamide, azathioprine, or other immunosuppressant  
  - Glucocorticoid (in addition to the above)

**Neuromyelitis optica (NMO)** | Rituxan® (rituximab) may be considered medically necessary for the treatment of neuromyelitis optica when:  
- The patient is refractory to at least one standard immunosuppressive drug (eg, azathioprine or mycophenolate mofetil).

**Primary Sjögren syndrome** | Rituxan® (rituximab) may be considered medically necessary for the treatment of primary Sjögren syndrome when:  
- Rituximab is used for patients refractory to glucocorticoids and other immunosuppressive agents (hydroxychloroquine and/or methotrexate), then any one of the following:  
  - Cyclophosphamide, or  
  - Mycophenolate, or
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><strong>Rituxan® (rituximab)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Medical Necessity</strong></td>
<td></td>
</tr>
</tbody>
</table>
| **Systemic lupus erythematosus (SLE)** | Rituxan® (rituximab) may be considered medically necessary for the treatment of systemic lupus erythematosus when: 
- Rituximab is used as add-on therapy for patients with the following: 
  - The patient has a confirmed diagnosis of SLE using either American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC) criteria. 
  - The patient has failed a 6-months trial of standard induction therapy with mycophenolate, cyclophosphamide, azathioprine, or other immunosuppressant, plus glucocorticoid. |
| **Systemic sclerosis (scleroderma)** | Rituxan® (rituximab) may be considered medically necessary for the treatment of systemic sclerosis when: 
- Rituximab is used for patients refractory to first-line treatment with cyclophosphamide or glucocorticoids. |
| **Autoimmune Dermatologic Diseases** | 
| **Pemphigoid diseases:** | Rituxan® (rituximab) may be considered medically necessary for the treatment of pemphigoid diseases in treatment-refractory patients when: 
- Standard initial treatment was tried and failed. Standard initial treatment includes at least two of the following: 
  - Glucocorticoids, azathioprine, mycophenolate, or dapsone |
| - Bullous pemphigoid | 
| - Mucous membrane pemphigoid (including ocular cicatricial pemphigoid) | 
| - Epidermolysis bullosa acquisita | 
| **Pemphigus diseases:** | Rituxan® (rituximab) may be considered medically necessary as a first line treatment in patients newly diagnosed with a pemphigus disease. 
- Pemphigus vulgaris 
- Pemphigus foliaceus 
- Paraneoplastic pemphigus |
| **Hematologic** | 
| **Autoimmune hemolytic anemias (AIHA)** | Rituxan® (rituximab) may be considered medically necessary for the treatment of autoimmune hemolytic anemias when: |
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>Warm AHIA</td>
<td>Rituximab is used to treat warm AIHA in glucocorticoid-refractory or glucocorticoid–dependent patients</td>
</tr>
<tr>
<td>Cold AHIA</td>
<td>Rituximab is used to treat cold agglutination syndrome.</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>Chronic graft-versus-host disease (GVHD)</td>
<td>Rituxan® (rituximab) may be considered medically necessary for the treatment of chronic GVHD when:</td>
</tr>
<tr>
<td></td>
<td>• Rituximab is used in patients refractory to glucocorticoids</td>
</tr>
<tr>
<td>Desensitization of human leukocyte antigen (HLA)</td>
<td>Rituxan® (rituximab) may be considered medically necessary for renal transplant candidates when:</td>
</tr>
<tr>
<td></td>
<td>• Rituximab is used in desensitization of HLA-sensitized renal transplant candidates prior to transplantation.</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>Rituxan® (rituximab) may be considered medically necessary in the treatment of hemophilia when:</td>
</tr>
<tr>
<td></td>
<td>• Rituximab is used as a factor inhibitor for patients who are refractory to conventional first-line treatments (eg, immune tolerance induction, glucocorticoids with or without cyclophosphamide).</td>
</tr>
<tr>
<td><strong>AND</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Rituximab is used as an add-on therapy</td>
</tr>
<tr>
<td>Idiopathic (immune) thrombocytopenic purpura</td>
<td>Rituxan® (rituximab) may be considered medically necessary second line therapy for the treatment of ITP when:</td>
</tr>
<tr>
<td>(ITP)</td>
<td>• Patients’ platelet counts continue to be at or less than 30,000 after first-line treatment using any one of the following:</td>
</tr>
<tr>
<td></td>
<td>o IVIG</td>
</tr>
<tr>
<td></td>
<td>o High-dose glucocorticoids</td>
</tr>
<tr>
<td></td>
<td>o Anti-D immunoglobulin</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura (TTP)</td>
<td>Rituxan® (rituximab) may be considered medically necessary for the treatment of TTP when:</td>
</tr>
<tr>
<td></td>
<td>• Rituximab is used in patients with refractory or relapsed disease (ie, lack of response to plasma exchange therapy and glucocorticoids).</td>
</tr>
<tr>
<td>Other</td>
<td>Rituxan® (rituximab) may be considered medically necessary</td>
</tr>
<tr>
<td>Multicentric Castleman</td>
<td>Rituxan® (rituximab) may be considered medically necessary</td>
</tr>
</tbody>
</table>
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.

disease (angiofollicular lymph node hyperplasia) for the treatment of multicentric Castleman disease.

Drug | Investigational
--- | ---
Rituxan® (rituximab) | Rituxan® (rituximab) is investigational for all other non-oncologic uses, including but not limited to:
- induction immunosuppressive therapy for kidney transplantation
- induction immunosuppressive therapy for heart transplantation
- mixed connective tissue disease
- multiple sclerosis
- paroxysmal cold hemoglobinuria
- prophylaxis for graft-versus-host disease
- treatment of antibody-mediated rejection after pancreatic islet transplantation
- treatment of antibody-mediated rejection in solid organ transplant recipients
- treatment of minimal change disease
- treatment of myasthenia gravis

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 1000 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 / m$^2$ once weekly for 4 weeks.</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>In combination with a tapering dose of glucocorticoids, dosing</td>
</tr>
</tbody>
</table>
Dosage and Quantity Limits

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage and Quantity Limit of Rituxan® (rituximab)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>is two 1000 mg IV infusions, separated by 2 weeks, then a 500 mg IV infusion at month 12 and every 6 months thereafter or based on clinical evaluation. Dose upon relapse is 1000 mg IV infusion with consideration to resume or increase the glucocorticoid dose based on clinical evaluation. Subsequent infusions may be no sooner than 16 weeks after the previous infusion.</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) (code terminated 1/1/19)</td>
</tr>
<tr>
<td>J9311</td>
<td>Injection, rituximab 10 mg and hyaluronidase (new code effective 1/1/19)</td>
</tr>
<tr>
<td>J9312</td>
<td>Injection, rituximab, 10 mg (new code effective 1/1/19)</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 (Biogen & Genentech, 2018).

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 lysed 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. 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:

- 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
- Bowel obstruction and perforation
- Not administering 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.
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. 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.

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.  

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 cicatrical 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, e.g., to lymphoma or lymphoproliferative disorders. Corticosteroids are first-line treatment in warm AIHA but less effective in cold AIHA.  

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 observations 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. 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). 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.\textsuperscript{18} For these patients, increased PE and/or addition of cyclosporine are current treatment options.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 (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.\textsuperscript{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 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.

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. 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.

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

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. 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. 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.

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)

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 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.

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.
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**

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 and 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, 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.

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 (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.

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**

**Graft-Versus-Host Disease**

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 (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.126

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

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

Antibody-mediated injury to allografts comprises ABMR, ABMR without complement deposition, antibody-mediated endarteritis, and accelerated arteriosclerosis of allografts.132 Induction immunosuppressive regimens initiated before, at the time of, or immediately after transplantation, mute T-cell responses to antigen presentation reduces acute rejection.133 Induction regimens typically are combination high-dose immunosuppressive agents or anti-T-cell antibodies (eg, antithymocyte globulin) plus lower dose immunosuppressive agents.
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.

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**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warm autoimmune hemolytic anemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01181154 (^a)</td>
<td>Rituximab in Adult's Warm Auto-Immune Hemolytic Anemia: a Phase III, Double-bind, Randomised Placebo-controlled Trial</td>
<td>32</td>
<td>Jan 2016 (completed)</td>
</tr>
<tr>
<td><strong>ANCA-associated vasculitis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02433522 (^a)</td>
<td>Extended Follow Up of the MAINRITSAN 2 Study. Comparison Between a Long Term and a Conventional Maintenance Treatment With Rituximab: a Placebo-Controlled Randomized Trial</td>
<td>97</td>
<td>Sep 2018 (ongoing)</td>
</tr>
<tr>
<td>NCT01697267</td>
<td>An International, Open Label, Randomised Controlled Trial Comparing Rituximab With Azathioprine as Maintenance Therapy in Relapsing ANCA-associated Vasculitis Rituximab Vasculitis Maintenance Study (RITZAREM)</td>
<td>190</td>
<td>Dec 2019</td>
</tr>
<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>NCT02198248</td>
<td>Low-dose Glucocorticoids Plus Rituximab Versus High-dose Glucocorticoids Plus Rituximab for Remission Induction in ANCA-associated Vasculitis; a Multicentre, Open Label, Randomised Control Trial</td>
<td>140</td>
<td>Sep 2020</td>
</tr>
<tr>
<td>Acquired hemophilia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01808911</td>
<td>Outcome of Acquired Hemophilia With Steroid Combined With Cyclophosphamide Versus Steroid Combined With Rituximab (CREHA Study)</td>
<td>164</td>
<td>Jun 2020</td>
</tr>
<tr>
<td>Immune thrombocytopenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03304288</td>
<td>The Combination of Low-dose Rituximab and All-trans Retinoic Acid as the Treatment of Steroid-resistant/Relapse Immune Thrombocytopenia: A Multicenter, Randomized, Open-label Trial</td>
<td>188</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02807103</td>
<td>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</td>
<td>108</td>
<td>Jun 2020</td>
</tr>
<tr>
<td>NCT03164473</td>
<td>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</td>
<td>98</td>
<td>Jul 2022</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01862926</td>
<td>A Randomized, Double Blind Controlled Trial Comparing Rituximab Against Intravenous Cyclophosphamide in Connective Tissue Disease Associated Interstitial Lung Disease</td>
<td>116</td>
<td>Nov 2020</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01748084</td>
<td>Evaluation of Rituximab in Systemic Sclerosis Associated Polyarthritis (RECOVER)</td>
<td>22</td>
<td>Apr 2016</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02950155</td>
<td>A Randomized, Double-Blind, Placebo-controlled Multicenter Study Evaluating the Safety and Efficacy of Rituximab (Mabthera®) in Patients With New Onset Generalized Myasthenia Gravis (MG)</td>
<td>60</td>
<td>Jun 2020</td>
</tr>
<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>NCT01955187</td>
<td>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)</td>
<td>106</td>
<td>Apr 2019</td>
</tr>
<tr>
<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 2019</td>
</tr>
<tr>
<td>NCT03018535</td>
<td>A Randomized Controlled Trial of Rituximab Versus Steroids and Cyclophosphamide in the Treatment of Idiopathic Membranous Nephropathy (RI-CYCLO)</td>
<td>70</td>
<td>Dec 2019</td>
</tr>
<tr>
<td>NCT01508468</td>
<td>Prospective Randomized Multicentric Open Label Study to Evaluate Rituximab Treatment for Idiopathic Membranous Nephropathy (IMN)</td>
<td>80</td>
<td>Sep 2016 (unknown)</td>
</tr>
</tbody>
</table>

### Unpublished

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01095172</td>
<td>A Randomized Trial of Rituximab in Induction Therapy for Living Donor Renal Transplantation</td>
<td>612</td>
<td>Oct 2023</td>
</tr>
</tbody>
</table>

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

* 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 treatment of lupus nephritis.148 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 and made the following recommendations157:

- 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.

**American Society of Hematology**

The American Society of Hematology (2011) published evidence-based guidelines on immune thrombocytopenia (ITP).\(^\text{149}\) Rituximab was suggested in the following clinical scenarios (all grade 2 suggestions based on level C evidence [randomized controlled trials with serious flaws, weaker observational studies, or indirect evidence]):

- “... children or adolescents with ITP who have significant ongoing bleeding despite treatment with IVIg [intravenous immunoglobulins], anti-D, or conventional doses of corticosteroids (Grade 2C).

- “... as an alternative to splenectomy in children or adolescents with chronic ITP or in patients who do not respond favorably to splenectomy (Grade 2C).”

- “...[adults with ITP] at risk of bleeding who have failed one line of therapy such as corticosteroid, IVIg, or splenectomy (Grade 2C).”.

The Society (2015) convened a panel of experts to review and revise the guidelines. Expected publication for its update is late 2018.
National Institute for Health and Care Excellence

Multiple Sclerosis

The National Institute for Health and Care Excellence (2014) updated its guidance on the management of multiple sclerosis in primary and secondary care. The guidance did not include rituximab.

Rheumatoid Arthritis

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. 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.

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.

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.

**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. 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.
American Academy of Neurology

Multiple Sclerosis

The American Academy of Neurology (2018) updated its guidelines on disease-modifying therapies for adults with multiple sclerosis. 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.

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. 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.\textsuperscript{136} 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)

Medicare National Coverage

There is no national coverage determination.

Regulatory Status

In 1997, rituximab (Rituxan® [Biogen; Genentech]) 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 Related Policies). Subsequent indications approved by FDA are summarized in Table 2.

Table 2. FDA-Approved Indications for Rituximab

<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  
- 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,”] |
<table>
<thead>
<tr>
<th>Date</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>- In combination with FC for the treatment of patients with previously untreated and previously treated CD20-positive CLL</td>
</tr>
<tr>
<td>2011</td>
<td>- 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</td>
</tr>
<tr>
<td></td>
<td>- In combination with glucocorticoids for the treatment of adult patients with Wegener granulomatosis and microscopic polyangiitis</td>
</tr>
</tbody>
</table>


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>
</tr>
<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>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>07/01/17</td>
<td>Formatting edit; added hyperlink menu for Medical Necessity Criteria sections.</td>
</tr>
<tr>
<td>02/14/18</td>
<td>Interim Review, approved February 13, 2018. Update hospital based outpatient coverage from 30 days to 90 days.</td>
</tr>
<tr>
<td>11/01/18</td>
<td>Minor update, the Site of Service criteria was updated for clarity.</td>
</tr>
<tr>
<td>01/01/19</td>
<td>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).</td>
</tr>
</tbody>
</table>

**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). ©2019 Premera All Rights Reserved.

**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.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5992. 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 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at:

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).

اردو (Urdu):
婆罗多族人也可以使用婆罗多族人的语言来了解这一信息。您也可以通过800-722-1471 (TTY: 800-842-5357) 联系电子邮件服务部以获得帮助。

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過Premera Blue Cross提出的申請或保險的重要訊息。本通知可能有重要的日期，您可能需要在截止日期之前採取行動，以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

Oromo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):
A vi sa a gen Enfòmasyon Enpòtan lod ann. A vi a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atraav Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sa a. Ou ka gen pou pran kék aksyon avan sèten dat limit pou ka kente kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou reseswa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Hmoob (Hmong):

Ilokano (Ilocano):
Daytoy a Pakdaak ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaak mabalin nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyonowo yenno coverange babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a pelta iti daytoy a pakdaak. Mabalin nga adda rumbeng nga aramideno nga adda sabbay dagiti partikular a naatidung nga adda taud mopan tapapatgalinea ito daytoage ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a manglega iti daytoy nga impormasion ken taglum iti bukodyo a pasagasa nga awan ti bayadanyo. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):