Rituximab for Non-Oncology Indications

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Related Coverage Resources

Oncology Indications

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

This coverage policy addresses the use of rituximab for non-oncology indications. The use of rituximab for oncology indications (including post-transplant lymphoproliferative disorder and Castleman’s disease) is addressed in a separate coverage policy. Please refer to the related coverage policy link above (Oncology Medications).

Rituximab (reference brand and biosimilars) is considered medically necessary when used for the treatment of any of the following indications when the associated criteria are met:

- Rheumatoid arthritis (RA) and the following criteria:
  - 18 years of age and older
  - Used in combination with methotrexate (unless contraindicated per FDA label or documented intolerance)
  - EITHER of the following:
    - History of a beneficial clinical response to rituximab (Rituxan)
    - BOTH of the following are met:
      - Failure or inadequate response, contraindication per FDA label, or documented intolerance to at least ONE disease-modifying anti-rheumatic drug (DMARD) (for example, methotrexate, leflunomide, sulfasalazine)
• Failure or inadequate response, contraindication per FDA label, documented intolerance, or not a candidate for ONE preferred anti-tumor necrosis factor (TNF) biologic therapy

• **Anti-Neutrophil Cytoplasmic Antibody-associated (ANCA-associated) vasculitides** when ANY of the following are met:
  o Granulomatosis with Polyangiitis (GPA) (Wegener Granulomatosis [WG])
  o Churg-Strauss Syndrome
  o Microscopic Polyangiitis (MPA)
  o Pauci-immune glomerulonephritis

• **Dermatomyositis or polymyositis** when BOTH of the following are met:
  o Documented diagnosis established by biopsy
  o Failure of standard medical therapy (corticosteroids AND immunosuppressants)

• **Factor inhibitors in an individual with hemophilia** refractory to conventional treatments (for example, Immune Tolerance Induction [ITI], steroids, cyclophosphamide)

• **Immune or Idiopathic Thrombocytopenia (ITP)** when the following is met:
  o Failure/inadequate response, contraindication per FDA label, or intolerance to at least one prior agent

• **Myasthenia gravis** (MG) when the following is met:
  o Failure/inadequate response, contraindication per FDA label, intolerance or not a candidate to TWO immunosuppressive agents (for example: azathioprine, cyclosporine, or methotrexate)

• **Neuromyelitis Optica** (NMO) when there is a documented diagnosis

• **Pediatric Nephrotic Syndrome** when ALL of the following are met:
  o Individual is 18 years of age or younger
  o Disease is relapsing and steroid-dependent
  o Failure or inadequate response, contraindication per FDA label, or documented intolerance to corticosteroid or immunosuppressive medication (for example, cyclophosphamide, cyclosporine, mycophenolate mofetil)

• **Pemphigus vulgaris and other refractory autoimmune blistering diseases** (for example, pemphigus foliaceus, bullous pemphigoid, cicatricial pemphigoid, epidermolysis bullosa acquisita, and paraneoplastic pemphigus)

• **Refractory autoimmune hemolytic anemia** (for example, corticosteroids, immunosuppressants, immunoglobulin)

• **Refractory chronic Graft versus Host Disease** (GvHD)

• **Solid organ transplant** when ONE of the following is met:
  o Desensitization for highly-allosensitized transplant candidates (to reduce HLA antibodies)
  o Antibody-mediated rejection (AMR)

• **Sjögren’s syndrome when the following is met:**
  o Individual has systemic manifestations (for example: cryoglobulinemia associated with vasculitis, vasculitis, severe parotid swelling, inflammatory arthritis, pulmonary disease)
  o Failure/inadequate response, contraindication per FDA label, intolerance or not a candidate to ONE immunosuppressive agent

• **Systemic Lupus Erythematosus (SLE) [Lupus]** when the following criteria are met:
• One of the following:
  • Individual has neuropsychiatric manifestations of SLE (for example: refractory acute confusional state or other psychiatric disorders (such as lupus psychosis), severe peripheral nervous system disorders (such as, polyneuropathy, mononeuropathy, plexopathy)
  • Individual has lupus nephritis
• Documented failure/inadequate response, intolerance, contraindication per FDA label, or not a candidate to ONE immunosuppressive agent (for example: azathioprine, cyclophosphamide, mycophenolic mofetil)

• Thrombotic thrombocytopenic purpura (TTP)

**EFFECTIVE 7/1/2020:**

Coverage for rituximab varies across plans. Refer to the customer’s benefit plan document for coverage details. Where coverage requires the use of preferred products, the following criteria apply.

For Employer Group Benefit Plans and Individual and Family Plans: Rituxan (rituximab) is covered when ONE of the following are met:

- History of beneficial clinical response with Rituxan (rituximab)
- Documented intolerance to Ruxience (rituximab-pvvr) AND Truxima (rituximab-abbs)

Initial authorization is up to 12 months.

Rituximab (reference brand and biosimilars) is considered medically necessary for continued use when the initial criteria are met.

Reauthorization for up to 12 months

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Rituximab (reference brand and biosimilars) is considered experimental, investigational or unproven for ANY other use including the following:

- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- IgG4-related disease
- Membranous Nephropathy
- Multiple Sclerosis (MS)
- Pediatric Acute-Onset Neuropsychiatric Syndrome/Pediatric Autoimmune Neuropsychiatric Disorders (PANS/PANDAS)

The use of rituximab and hyaluronidase human (Rituxan Hycela™) is not covered for any non-oncology indication because it is considered experimental, investigational, or unproven.

**Note:** Receipt of sample product does not satisfy any criteria requirements for coverage.

**FDA Approved Indications**

**FDA Approved Indication**

**Non–Hodgkin’s Lymphoma (NHL)**

Rituxan is indicated for the treatment of patients with:

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to Rituxan in combination with chemotherapy, as single-agent maintenance therapy
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens

**Chronic Lymphocytic Leukemia (CLL)**
Rituxan is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL.

**Rheumatoid Arthritis (RA)**
Rituxan in combination with methotrexate is indicated for the treatment of adult patients with moderately- to severely-active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

**Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA)**
Rituxan, in combination with glucocorticoids, is indicated for the treatment of adult patients with Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA).

**Pemphigus Vulgaris (PV)**
Rituxan is indicated for the treatment of adult patients with moderate to severe pemphigus vulgaris.

**Limitations of Use:**
Rituxan is not recommended for use in patients with severe, active infections.

**Recommended Dosing**

**FDA Recommended Dosing**

**Non–Hodgkin’s Lymphoma (NHL)**
The recommended dose is 375 mg/m² as an intravenous infusion according to the following schedules:

- **Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL** - Administer once weekly for 4 or 8 doses.
- **Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL** - Administer once weekly for 4 doses.
- **Previously Untreated, Follicular, CD20-Positive, B-Cell NHL** - Administer on Day 1 of each cycle of chemotherapy, for up to 8 doses. In patients with complete or partial response, initiate Rituxan maintenance eight weeks following completion of Rituxan in combination with chemotherapy. Administer Rituxan as a single-agent every 8 weeks for 12 doses.
- **Non-progressing, Low-Grade, CD20-Positive, B-cell NHL, after first-line CVP chemotherapy** - Following completion of 6–8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses.
- **Diffuse Large B-Cell NHL** - Administer on Day 1 of each cycle of chemotherapy for up to 8 infusions.

**Chronic Lymphocytic Leukemia (CLL)**
The recommended dose is 375 mg/m² the day prior to the initiation of FC chemotherapy, then 500 mg/m² on Day 1 of cycles 2–6 (every 28 days).

**Recommended Dose as a Component of Zevalin® for treatment of NHL**
Infuse rituximab 250 mg/m2 within 4 hours prior to the administration of Indium-111-(In-111-) Zevalin and within 4 hours prior to the administration of Yttrium-90-(Y-90-) Zevalin. Administer Rituxan and In-111-Zevalin 7–9 days prior to Rituxan and Y-90-Zevalin. Refer to the Zevalin package insert for full prescribing information regarding the Zevalin therapeutic regimen.
Rheumatoid Arthritis (RA)
Administer Rituxan as two 1000 mg intravenous infusions separated by 2 weeks. Glucocorticoids administered as methylprednisolone 100 mg intravenous or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion reactions. Subsequent courses should be administered every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks. Rituxan is given in combination with methotrexate.

Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA)
Induction Treatment of Patients with Active GPA/MPA
Administer Rituxan as a 375 mg/m$^2$ intravenous infusion once weekly for 4 weeks for patients with active GPA or MPA.

Glucocorticoids administered as methylprednisolone 1000 mg intravenously per day for 1 to 3 days followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day and tapered per clinical need) are recommended to treat severe vasculitis symptoms. This regimen should begin within 14 days prior to or with the initiation of Rituxan and may continue during and after the 4 week induction course of Rituxan treatment.

Follow up Treatment of Patients with GPA/MPA who have achieved disease control with induction treatment
Administer Rituxan as two 500 mg intravenous infusions separated by two weeks, followed by a 500 mg intravenous infusion every 6 months thereafter based on clinical evaluation.

Patients should receive 100 mg intravenous methylprednisolone to be completed 30 minutes prior to each Rituxan infusion.

If induction treatment of active disease was with Rituxan, follow up treatment with Rituxan should be initiated within 24 weeks after the last Rituxan induction infusion or based on clinical evaluation, but no sooner than 16 weeks after the last Rituxan induction infusion.

If induction treatment of active disease was with other standard of care immunosuppressants, Rituxan follow up treatment should be initiated within the 4 week period that follows achievement of disease control.

Pemphigus Vulgaris (PV)
Administer Rituxan as a two 1000 mg intravenous infusions separated by 2 weeks in combination with a tapering course of glucocorticoids.

Maintenance treatment- administer as a 500 mg intravenous infusion at month 12 and every 6 months thereafter or based on clinical evaluation.

Treatment of relapse- administer as a 1000 mg intravenous infusion on relapse, and consider resuming or increasing the glucocorticoid dose based on clinical evaluation.

Drug Availability
Rituximab vials are available in 100 mg/10 mL and 500 mg/50 mL strengths.

General Background
Pharmacology
Rituximab is a chimeric monoclonal antibody directed against transmembrane CD20 proteins on the surface of immature and mature B lymphocytes. The effect of rituximab binding to these proteins is cell lysis and a reduction in antibody-producing capacity. This results in a lowered autoimmune activity in RA. Infusions of rituximab in patients with RA have less variability than patients with lymphoma.

Professional Societies/Organizations
Active Rheumatoid Arthritis
American College of Rheumatology (ACR)

American College of Rheumatology (ACR) 2015 Guideline for the Treatment of Rheumatoid Arthritis

In the ACR guidelines, anti–tumor necrosis factor (anti-TNF) biologics include the following: Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Remicade (infliximab), and Simponi (golimumab). Non-TNF biologics include the following: Actemra (tocilizumab), Orencia (abatacept), and Rituxan (rituximab). DMARD agents include the following: methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine (excludes azathioprine, cyclosporine, minocycline, and gold).

Guidelines from the American College of Rheumatology (ACR) [2015] have tumor inhibitors and non-TNF biologics (including rituximab), equally positioned following a trial of a conventional synthetic DMARD.

Early disease recommendations (defined as <6 months)
For patients with low disease activity and in those who have not taken a DMARD, the guidelines recommend to use DMARD monotherapy (Methotrexate preferred) over double therapy or triple therapy (Recommendation: strong; Level of evidence: Low). If the disease activity remains moderate or high despite monotherapy with a DMARD, use combination DMARDs or use a TNF inhibitor or a non-TNF inhibitor biologic (all options are with or without methotrexate and given in no preference order) rather than continuing monotherapy with a DMARD (Recommendation: strong; Level of evidence: Low). If the disease activity remains moderate or high despite DMARDs, the guidelines suggest use of monotherapy with a TNF inhibitor over monotherapy with tofacitinib (Level of evidence: Low) or use a TNF inhibitor with methotrexate over tofacitinib with methotrexate (Level of evidence: Low).

Established disease recommendations (defined as >6 months)
For patients with low disease activity and those who have not taken a DMARD, the guideline recommends use of monotherapy with a DMARD (methotrexate preferred) over a TNF inhibitor (Recommendation: Strong; Level of evidence: Low). If the disease activity remains moderate or high despite monotherapy with a DMARD, use combination traditional DMARDs or add a TNF inhibitor or a non-TNF inhibitor biologic (all options are with or without methotrexate and given in no preference order) rather than continuing monotherapy with a DMARD (Recommendation: Strong; Level of evidence: Moderate to very low). If the disease activity remains moderate or high despite TNF inhibitor in patients who are not currently on a DMARD, add one or two DMARDs to a TNF inhibitor rather than continuing monotherapy with a TNF inhibitor (Level of evidence: High).

Conditional recommendations for established RA disease:
- If the disease activity remains moderate/high despite the use of non-TNF biologic, use another non-TNF biologic (with or without methotrexate) over tofacitinib (with or without methotrexate) (Level of evidence: Very low).
- If the disease activity remains moderate/high despite use of multiple (defined as 2+) sequential TNF inhibitors, use tofacitinib (with or without methotrexate) over another TNF inhibitor (with or without methotrexate) if the use of a non-TNF biologic is not a treatment option (Level of evidence: Low).
- If the disease activity remains moderate/high despite use of TNF inhibitor and at least one non-TNF biologic, the guideline recommends to first use another non-TNF biologic (with or without methotrexate) over tofacitinib or use tofacitinib (with or without methotrexate) over another TNF inhibitor agent (Level of evidence: Very low).

Recommendations for specific high-risk conditions:
- Congestive Heart Failure (CHF): ACR guidelines recommend using combination DMARDs or a non-TNF biologic agent or tofacitinib over TNF inhibitors (conditional recommendation; Level of evidence: Moderate to very low). If there is CHF worsening on a current TNF inhibitor, ACR recommends use of a combination DMARD or non-TNF biologic or tofacitinib over another TNF inhibitor (conditional recommendation; Level of evidence: Very low).
- Previously treated lymphoproliferative disorder: ACR guidelines recommend using rituximab over TNF inhibitor (Recommendation: Strong; Level of evidence: Very low) or use combination DMARD or abatacept or tocilizumab over TNF inhibitor (conditional recommendation; Level of evidence: Very low).
• Previous serious infection: ACR guidelines recommend using combination DMARD over TNF inhibitor or use abatacept over TNF inhibitor (conditional recommendation; Level of evidence: Very low). (Singh, 2016)

Anti-Neutrophil Cytoplasmic Antibody-associated (ANCA-associated) Vasculitides
European League Against Rheumatism, European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA)

EULAR/ERA-EDTA recommendations for ANCA-associated vasculitis mention rituximab in combination with low-dose corticosteroids as a potential treatment option for remission-maintenance therapy. Remission-maintenance therapy is recommended for at least 24 months following induction of sustained remission. (Yates, 2016)

National Institute for Health and Care Excellence (NICE)
NICE guidelines suggest rituximab administered concomitantly with glucocorticoids as an option to actuate a remission in adults with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, under certain conditions, which include: additional cyclophosphamide use would surpass the maximum cumulative cyclophosphamide dose recommendation; the individual has a contraindication to or is intolerant of cyclophosphamide; the individual has fertility concerns with cyclophosphamide treatment, or the disease has continued to be active or is progressing, even though there has been a cyclophosphamide course of 3-6 months; the individual has a history of uroepithelial malignancy. (NICE 2014)

Factor Inhibitors in Hemophilia
Inhibitors (i.e., antibodies) in hemophilia refer to IgG antibodies that neutralize clotting factors. Antibodies include alloantibodies (i.e., antibodies to replacement infused factor VIII or factor IX) and autoantibody inhibitors which occur spontaneously in individuals with previously normal hemostasis and directed against a “self” clotting factor, most commonly factor VIII. Replacement factors are used as prophylaxis and treatment of bleeding episodes in hemophiliacs. The development of inhibitory antibodies against infused factors is a major complication in the treatment of patients with hemophilia. The same principles of replacement therapy for alloantibodies apply to acquired autoantibody inhibitors. Treatment of inhibitors (alloantibodies/autoantibodies) typically involves immune tolerance induction (ITI) and/or depletion/suppression of inhibitors using immunomodulatory agents such as steroids (e.g., prednisone), cytotoxic agents (e.g., cyclophosphamide) and IVIG.

British Society for Haematology (BSH)
British Society for Haematology published guidelines for the diagnosis and treatment of factor VIII and IX inhibitors in congenital hemophilia. Recommendations include immune toleration induction for patients with severe hemophilia A and a persistent inhibitor that interferes with prophylaxis or treatment of bleeds at standard doses of FVIII. The guideline provides additional details around ITI and indicates that if there is an inadequate decrease in the inhibitor titer (20% reduction over a 6 month period), an alternative strategy may be considered. Options referenced include FVIII dose increase, the introduction of pdFVIII, immunosuppression with rituximab or stopping ITI (Grade 2C). (Collins, 2013b)

The United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO) provides guidelines approved by the British Committee for Standards in Haematology for acquired hemophilia with inhibitors. Rituximab is recommended as a first-line agent when there is a contraindication to standard immunosuppression (i.e., prednisone or cyclophosphamide). Rituximab is a second-line agent if there is no response after 3-5 weeks of treatment with standard immunosuppression. (Collins, 2013a)

Graft vs. Host Disease
British Society for Haematology (BSH)
British Society for Haematology Guidelines on acute graft versus host disease recommends against the use of rituximab. (Dignan, 2012a) Guidelines for treatment of chronic graft versus host disease (GvHD) suggests rituximab as a second line treatment option in refractory cutaneous or musculoskeletal chronic GvHD (strength of recommendation = 2B or weak and based on moderate quality evidence) and as third line treatment in chronic GvHD involving other organs (strength of recommendation = 2C or weak and based on low quality evidence). (Dignan, 2012b)
**Immune or Idiopathic Thrombocytopenia**  
**American Society of Hematology (ASH)**
For children or adolescents with ITP, rituximab is a second-line treatment for patients with significant ongoing bleeding despite treatment with intravenous immune globulin (IVIG), anti-D immunoglobulin, or conventional doses of corticosteroids; as an alternative to splenectomy in chronic ITP; or for patients who do not respond favorably to splenectomy. For adults with ITP, rituximab may be considered for patients at risk of bleeding who have failed at least one of the following: corticosteroids, IVIG, or splenectomy. (Neunert, 2011)

**Neuromyelitis Optica (NMO)**  
**International Panel for NMO Diagnosis**
Diagnostic criteria from Wingerchuk et al have been confirmed (Saiz, 2007) and note that the NMO IgG is a highly specific marker in diagnosing the disease. The criteria state CNS involvement beyond the optic nerves and spinal cord is compatible with NMO and that the following are criteria recommended for diagnosing NMO: presence of optic neuritis and myelitis with 2 of 3 supportive criteria - MRI evidence of a contiguous spinal cord lesion 3 or more segments in length, onset brain MRI non-diagnostic for MS, and NMO-IgG seropositivity. (Wingerchuk, 2006)

In 2015, the International Panel for NMO Diagnosis was convened and the 2006 consensus criteria were updated to new nomenclature (neuromyelitis optica spectrum disorders [NMOSD]) and provide specific criteria based on the presence of aquaporin-4 immunoglobulin G (AQP4-IgG). (Wingerchuk, 2015)

**American Academy of Neurology (AAN)**
The AAN’s guideline on clinical evaluation and treatment of transverse myelitis (TM) assessed the evidence for diagnostic tests and therapies for TM and made evidence-based recommendations. The guidelines note that rituximab may be effective and considered to reduce relapses in patients with neuromyelitis optica (NMO). (Scott, 2011)

**European National Neurological Societies (EFNS)**
The EFNS (2010) panel recommendations for immunosuppressive treatment of neuromyelitis optica (NMO) suggest Rituxan as first-line therapy as follows:
- Azathioprine oral 2.5–3 mg/kg/day plus oral prednisolone 1 mg/kg/day, tapered when azathioprine becomes effective (after 2–3 months)  OR
- Rituximab [Option 1: i.v. 375 mg/m2 weekly for 4 weeks (lymphoma protocol); Option 2: 1000 mg infused twice, with a 2-week interval between the infusions (rheumatoid arthritis protocol); Options 1 and 2: re-infusion after 6–12 months; however, optimal treatment duration unknown] (Sellner, 2010)

**Pediatric Nephrotic syndrome**  
**Kidney Disease Improving Global Outcomes (KDIGO)**
Various clinical practice guidelines have been published by KDIGO are described as either “recommendations” (Level 1) or “suggestions” (Level 2) and rate the supporting evidence from A to D (A= High quality of evidence; B=Moderate; C=Low; D=Very Low). Recommendations include implications stating that most patients should receive the recommended course of action while suggestions imply that different choices will be appropriate for different patients. In the Clinical Practice Guidelines for Glomerulonephritis, for steroid sensitive nephrotic syndrome (SSNS) in children, KDIGO suggests the use of rituximab be confined to cases of steroid-dependent, (SSNS), where the individual experiences frequent relapses, regardless of the use of the most favorable regimens of prednisone and corticosteroid-sparing agents, and/or who have experienced serious adverse effects of medication therapy. (KDIGO, 2012)

**Sjogren’s Syndrome**  
**Sjogren’s Syndrome Foundation and the American College of Rheumatology (ACR)**
Sjogren’s Syndrome Foundation clinical practice guidelines state that rituximab use for keratoconjunctivitis sicca (KCS) and xerostomia is considered weak evidence. The guideline states moderate evidence for rituximab as therapeutic option for systemic manifestation in Sjogren’s syndrome. The guidelines define systemic manifestations as: Cryoglobulinemia associated with vasculitis, Vasculitis, Severe parotid swelling, Inflammatory arthritis, Pulmonary disease, peripheral neuropathy, especially mononeuritis. (Carsons, 2017)
Solid Organ Transplant
International Society of Heart and Lung Transplantation (ISHLT)
The ISHLT published guidelines for the care of heart transplant recipients states that most of the recommendations only achieve a level of evidence C indicating that recommendations are based on expert consensus and not on randomized controlled clinical trials. These guidelines include recommendations for the risk-assessment and prophylaxis strategies for allosensitized candidates. Desensitization therapy should be considered when the calculated panel reactive antibody (PRA) is considered by the individual transplant center to be high enough to significantly decrease the likelihood for a compatible donor match or to decrease the likelihood of donor heart rejection where unavoidable mismatches occur. Choices to consider as desensitization therapies include IVIG infusion, plasmapheresis, either alone or combined, rituximab, and in very selected cases, splenectomy. (Recommendation IIb and C level of evidence). The guidelines state that a large randomized controlled clinical trial is needed to assess the effectiveness of desensitization strategies and their impact on outcomes after HT. Class IIb is defined as “Usefulness/efficacy is less well established by evidence/opinion.” C Level of evidence is defined as “Consensus of opinion of the experts and/or small studies, retrospective studies, registries.” (Costanzo, 2010)

The ISHLT includes recommendations for the treatment of antibody-mediated rejection with initial therapy of AMR including immunoadsorption and corticosteroid or plasmapheresis/low dose of IVIG and corticosteroid. Rituximab can be added to reduce the risk of recurrent rejection. (Recommendation IIa and C level of evidence) Class IIa is defined as “Weight of evidence/opinion is in favor of usefulness/efficacy.” (Costanzo, 2010)

Kidney Disease Improving Global Outcomes (KDIGO)
KDIGO published a clinical practice guideline for the care of kidney transplant recipients. KDIGO recommends corticosteroids for the initial treatment of acute cellular rejection. The guideline suggests treating antibody-mediated acute rejection with one of the following alternatives, with or without corticosteroids (plasma exchange; intravenous immunoglobulin; anti-CD20 antibody (rituximab); lymphocyte-depleting antibody.)-2C It is stated that therapeutic strategies that include combinations of plasma exchange to remove donor-specific antibody, and/or IVIG and rituximab to suppress donor-specific antibody production have been used to successfully treat acute humoral rejection. However, the optimal protocol remains to be determined. There are no RCTs with adequate statistical power to compare the efficacy of these different strategies. (KDIGO, 2009)

Systemic Lupus Erythematosus
European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR)
EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations mention rituximab as a therapeutic option for patients with neuropsychiatric SLE refractory to standard immunosuppressive therapies. (Bertsias, 2010) Rituximab is used in patients with a refractory acute confusional state or other psychiatric disorders (e.g., lupus psychosis), and in severe peripheral nervous system disorders (e.g., polyneuropathy, mononeuropathy, acute inflammatory demyelinating polyradiculoneuropathy, myasthenia gravis, plexopathy). EULAR in combination with the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) has recommendations for the management of adult and pediatric lupus nephritis. (Bertsias, 2019) Rituximab is an alternative for patients who do not respond to first-line therapies. ACR recommendations for management of lupus nephritis note that rituximab may be appropriate in certain patients with lupus nephritis who have tried mycophenolate mofetil and cyclophosphamide and in patients whose nephritis fails to improve or worsens following 6 months of one induction therapy (Hahn, 2012).

Thrombotic thrombocytopenic purpura (TTP)
British Society for Haematology (BSH)
In the 2012 Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies, BSH recommends rituximab along with plasma exchange and corticosteroids for acute disease with cardiac or neurologic pathology, or for patients with refractory or recurrent immune-mediated disease. (Scully 2012)
The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative
No recommendations are available for Rituximab (Rituxan®).

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)
There are no CMS National Coverage Determinations for Rituximab (Rituxan®).

Clinical Efficacy
Active Rheumatoid Arthritis
The long-term safety of rituximab has been reported and includes 1,246 patients with over 5 years of follow-up. The overall serious infection rate was 3.76 per 100 patient-years. There was no observed increased risk of malignancy. (van Vollenhoven, 2015)

Anti-Neutrophil Cytoplasmic Antibody-associated (ANCA-associated) Vasculitides
The RAVE trial enrolled 197 patients with Wegener’s granulomatosis or microscopic polyangiitis. Rituximab was found to be non-inferior, but not superior, to a control regimen of cyclophosphamide with a switch to azathioprine if in remission after 3 months in achieving the primary endpoint (a Birmingham Vasculitis Activity Score for Wegener’s Granulomatosis (BVAS/WG) of 0 and successful completion of the prednisone taper at 6 months). For individuals with relapsing disease at baseline, 67% of patients on rituximab and 42% on the control regimen met the primary endpoint (p = 0.01). (Stone, 2010)

Pemphigus vulgaris and Autoimmune Blistering Diseases
Autoimmune blistering diseases (e.g., pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, cicatricial pemphigoid, epidermolysis bullosa acquisita, and paraneoplastic pemphigus) are rare and treatment with corticosteroids and immunosuppressive agents may not control disease. (Ferri, 2012; Cleveland Clinic, 2010; Habif, 2009).

Off Label Uses
Autoimmune Hemolytic Anemia
Autoimmune hemolytic anemia, an uncommon condition which may be idiopathic or secondary to another diagnosis involves the production of autoantibodies and the hemolysis of red blood cells (RBCs). AIHA may be classified as warm autoimmune hemolytic anemia or cold agglutinin disease. Treatment may include corticosteroids, immunosuppressants, immunoglobulin and splenectomy. Standard medical textbooks indicate that almost all treatments in AIHA are based on experience and opinion and not on evidence. Rituximab is described as generally accepted for treatment of refractory patients. The typical dosing regimen referenced is 375 mg/m² intravenously once weekly for 4 weeks. (Bope, 2012; Hoffman, 2012; Goldman, 2011)

Dermatomyositis and Polymyositis
The Rituximab in Myositis (RIM) trial included 200 adults with definite or probable dermatomyositis (DM) or polymyositis (PM) and juveniles at least 5 years of age with definite or probable DM. Individuals were refractory to glucocorticoids and at least 1 other immunosuppressant/immunomodulator. Patients were randomized to either rituximab “early” (at weeks 0 and 1) or rituximab “late” (at weeks 8 and 9). The primary endpoint evaluated time to improvement between the early and late rituximab groups, which did not differ significantly (20.0 weeks vs. 20.2 weeks, respectively, p = 0.74). Majority of patients (83%) met the definition of improvement by week 44 and the mean prednisone dose was decreased from 20.8 mg/day to 14.4 mg/day in 160 patients taking steroids at baseline (p < 0.0001). (Oddis, 2013)

Factor Inhibitors in Hemophilia
Inhibitors (i.e., antibodies) in hemophilia refer to IgG antibodies that neutralize clotting factors. Antibodies include alloantibodies (i.e., antibodies to replacement infused factor VIII or factor IX) and autoantibody inhibitors which occur spontaneously in individuals with previously normal hemostasis and directed against a “self” clotting factor, most commonly factor VIII. Replacement factors are used as prophylaxis and treatment of bleeding episodes in hemophiliacs. The development of inhibitory antibodies against infused factors is a major complication in the treatment of patients with hemophilia. The same principles of replacement therapy for alloantibodies apply to acquired autoantibody inhibitors. Treatment of inhibitors (alloantibodies/autoantibodies) typically involves
immune tolerance induction (ITI) and/or depletion/suppression of inhibitors using immunomodulatory agents such as steroids (e.g., prednisone), cytotoxic agents (e.g., cyclophosphamide) and IVIG.

A systematic review was conducted to examine the use of rituximab for the treatment of inhibitors in individuals with inherited severe hemophilia A or B. No randomized controlled trials were identified. The authors note that evidence is limited to case reports and case series. (Liu, 2015)

A summary and analysis of 29 studies, including 49 case reports, showed that a durable complete remission was obtained in 53% of cases and no severe adverse effects were related to rituximab. (Franchini, 2008) A national survey of 23 comprehensive care hemophilia centers in the United Kingdom reported 15 consecutive severe (<1% FVIII) hemophilia A patients with loss of detectable inhibitor in 40% of patients on rituximab in conjunction with ITI, but a lasting response was only seen in 2 patients (Collins, 2009).

**Graft vs. Host Disease**

Graft-versus-host disease (GVHD) is a common complication of allogeneic hematopoietic stem-cell transplantation (HSCT); it may also be seen after solid organ transplantation. In GVHD, activated T-cells attack transplanted hematopoietic stem cells or solid organs. Treatment depends on the extent of disease and may include steroids, calcineurin inhibitors, immunosuppressants, T-cell depleting agents and extracorporeal photopheresis. Currently, no single therapy is effective in the treatment of refractory, systemic acute and chronic graft-versus-host disease.

Chronic graft-versus-host disease (cGVHD) is the leading cause for late morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HSCT). Primary treatment of cGVHD is based on controlled trials and consists of prednisone given with or without a calcineurin inhibitor (CNI) whereas evidence in steroid refractory cGVHD is limited to phase II trials or retrospective analyses. (Wolff, 2011)

A systematic review and meta-analysis of rituximab for steroid-refractory cGVHD was performed. Six studies met inclusion criteria (with one study added following suggestion from an expert) including 3 prospective and 4 retrospective studies. No randomized controlled trials were located. The data suggest that rituximab is effective in treating cutaneous cGVHD; however, the response to rituximab appears to be less pronounced in other organs (oral mucosa, liver, gastrointestinal, lung, ocular, musculoskeletal). The authors state that the totality of the evidence generated through this systematic review demonstrates the gaps in the existing evidence base related to the efficacy of rituximab in treating patients with steroid-refractory cGVHD and describe the need for well-designed and adequately powered prospective studies. (Kharfan-Dabaja, 2009)

The results of a prospective, multicenter phase II study of weekly rituximab 375 mg/m² for 4 weeks followed by monthly rituximab for 4 months in 37 patients were reported. The overall response rate was 86% and the complete response rate was 22% with higher response rates in skin, oral cavity, and musculoskeletal systems than in other organs. 21 patients (57%) maintained their response, and 6 patients (16%) had steroid treatment successfully withdrawn. The results were encouraging; however, infectious complication and primary disease relapse accounted for the majority of treatment failure. The authors concluded that rituximab could improve clinical responses and quality of life of patients with steroid-refractory chronic graft-versus-host disease, although such patients may need active prophylaxis against infection. (Kim, 2010)

A Consensus Conference on Clinical Practice in Chronic GVHD aimed to summarize the currently available evidence for second-line treatment and to provide practical guidelines for the use of treatment modalities. Rituximab is identified as a second-line treatment option with a C-2 recommendation (Use in greater than second-line treatment justified) with evidence rating of II [Definition: Evidence from >1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferable from >1 center) or from multiple time series, or dramatic results from uncontrolled experiments]. Rituximab is recommended as a “reasonable second-line therapy of cGVHD, especially with sclerodermatous, lichenoid cutaneous disease as well as autoantibody-mediated cytopenias. The active dose is stated to still be a matter of debate and should be further investigated in prospective studies. (Wolff, 2011)
Medical textbooks describe the use of several agents, including rituximab as having variable success and being beneficial in patients refractive to standard therapy although further controlled clinical trials are warranted. (DeVita, 2011; Irwin, 2011; Kleigman, 2011)

**Pediatric Nephrotic syndrome**

A non-inferiority trial of rituximab was conducted in steroid-dependent nephrotic syndrome (SDNS) individuals, aged 1-16 years. These children were randomized to either 1 month of prednisone monotherapy or prednisone plus a 1 time dose of intravenous rituximab, and both groups had the steroid tapered after 1 month. At 3 months, there was a 42% reduction in proteinuria in the rituximab arm. Within 6 months, all but one participant had relapsed in the control group, while the median time to relapse was 18 months in the active treatment group. (Ravani, 2015)

A randomized, double-blind, placebo-controlled trial was conducted in children who were experiencing a relapse in either their frequently relapsing nephrotic syndrome (FRNS) or steroid dependent nephrotic syndrome (SDRS). Participants were randomized equally to either rituximab or placebo and were dosed once weekly for 4 weeks. The study duration was 53 weeks. The primary endpoint was the relapse-free period, which was defined as the time from randomization to the time of the first relapse once study treatment was initiated. Data demonstrated a significantly longer median relapse-free period in the rituximab arm as compared to the placebo arm. After randomization, individuals in the rituximab arm had significantly lower doses of steroid, while the steroid dosing in the placebo arm did not decrease significantly. Analyses indicated that the percentage of participants who could have withdrawn steroids was comparable between the two treatment arms, but the median time to first relapse after discontinuation of steroids significantly favored the rituximab treatment group. Nineteen months after randomization, all trial subjects had relapsed. The authors mention that the abbreviated observation period might be a limitation to understanding the long term risk of rare or serious adverse events in this group (e.g., progressive multifocal leukoencephalopathy). (Iijima, 2014).

A non-inferiority was conducted comparing treatment with rituximab plus lower dose prednisone and calcineurin inhibitors versus standard doses of these drugs in their ability to sustain 3-month proteinuria at baseline levels or up to 1 GM/day greater. Results demonstrated the 3 month proteinuria was reduced 70% in the Rituxan treatment arm compared to standard treatment. Fifty percent of the individuals in the Rituxan treatment arm were in remission and were able to discontinue medications, after 9 months. The authors conclude this data demonstrated that rituximab administered concomitantly with lower doses of prednisone and calcineurin inhibitors are non-inferior to standard treatment and able to support short-term remission in cases of INS dependent on both drugs, which facilitated their short-term discontinuation. (Ravani, 2011)

**Solid Organ Transplant**

**Desensitization and Antibody-Mediated Rejection (AMR)**

Sensitization to human leukocyte antigens (HLA) is a major barrier to transplantation for patients who have developed anti-HLA antibodies through pregnancy, transfusions, or prior transplants. Allosensitization prolongs the wait time for transplant and increases the risk of post-transplantation complications. Current desensitization therapies described in medical textbooks and the published literature include intravenous immunoglobulin (IVIG), IVIG combined with rituximab, and plasma exchange/plasmapheresis with or without IVIG.

**Desensitization**

The efficacy, outcomes and cost-effectiveness of desensitization using high-dose IVIG and rituximab were examined in 207 highly sensitized patients. Efficacy results/data were compared with end stage renal disease (ESRD) patients listed on the UNOS wait list/dialysis treatment. Parameters examined included efficacy of sensitization; patient and graft survival; survival rates on dialysis versus highly sensitized transplantation; acute rejection rate; and cost of desensitization versus dialysis at 36 months. Of the 207, 146 (71%) were transplanted. At 48 months, patient and graft survival were 95% and 87.5% respectively. Estimated patient survival at the end of 3 years was 96.6% for patients in the desensitized group compared with 79% for an age, end-stage renal disease etiology, and PRA matched group of patients remaining on dialysis during the study period. The authors concluded that desensitization with IVIG + rituximab is clinically and cost-effective with an estimated 17.6% greater probability of 3-year survival associated with desensitization versus dialysis alone. (Vo, 2013)
The efficacy of IVIG and rituximab administered to 76 HLA-sensitized individuals prior to kidney transplantation to reduce anti-HLA antibodies was evaluated. Participants were considered high immunologic risks with panel reactive antibody (PRA) 30%-79% in 25% of individuals and PRA > 80% in 75% or participants. 31 individuals received living donor (LD) and 45 received deceased donor (DD) transplants. Data from 39 individuals show mean pretreatment class I PRA was 79.7% ± 25.6% versus post-treatment 67.1% ± 28.6% (P=0.0001). Deceased donor recipients had a mean waiting list time of 95 ± 46 months prior to desensitization, but received transplants within 4 months after receiving IVIG plus rituximab combination treatment. Acute rejection occurred in 37% of participants (29%-AMR and 8% cell mediated rejection (CMR)). Nine experienced graft losses, with AMR involved in 6 cases. Patient and graft survivals up to 24 months were 95% and 84% respectively. The authors concluded that IVIG and rituximab seems to offer significant benefits in reduction of anti-HLA antibodies allowing improved rates of transplantation for highly sensitized patients, especially those awaiting DD, with acceptable antibody-mediated rejection and survival rates at 24 months. Outcomes are stated to be similar to those observed in nonsensitized patients and superior to patients who remain on dialysis for extended periods. The authors report that the results of this study are encouraging and support further analysis in a randomized controlled trial. (Vo, 2010)

There is limited available literature on strategies to treat allosensitization in cardiac transplant candidates and much of the current therapeutic practices are derived from experience with the transplantation of other solid organs, including the use of rituximab in treating allosensitized renal transplant candidates. Further data are needed to determine the usefulness of rituximab in allosensitized transplant candidates. (Velez, 2009)

### Antibody-Mediated Rejection (AMR)

A systematic review was conducted to determine the efficacy of a variety of treatments for acute AMR in renal allografts including plasmapheresis; immunoadsorption; IVIG; bortezomib; corticosteroids; anti-thymocyte preparations; eculizumab; mycophenolate; rituximab; cyclophosphamide; deoxyspergualin; splenectomy; and tacrolimus. There were no RCTs for rituximab identified by these authors. The authors concluded that there is insufficient evidence to adequately guide the treatment of AMR; relevant RCTs were of low quality; the data describing the efficacy of treatments for AMR in renal allografts are of low or very low quality; and that randomized controlled trials and dose-response studies are required. It is stated that controlled but nonrandomized studies supported the effect of rituximab, plasmapheresis (plasma exchange, PP), and bortezomib with some studies using a combination of these therapies so that the relative importance of an individual treatment could not be determined. (Roberts, 2012)

A prospective, open label, randomized study of rituximab versus standard of care immunosuppression (thymoglobulin and/or pulsed steroids) for treatment of biopsy confirmed acute transplant rejection in 20 consecutive pediatric renal transplant recipients (2-23 years) reported 1 year outcomes. Patients were randomized to standard of care rejection therapy (control immunosuppression group-CIS; steroid pulsing and/or thymoglobulin therapy for steroid-resistant rejection) versus standard of care therapy combined with four doses of rituximab (rituximab immunosuppression group-RIS). Thymoglobulin at 1.5mg/kg/dose for six doses was administered concomitant with steroid pulses and rituximab. Patient survival was 100% in both groups; there was no statistically significant difference in the mean time of AR after transplantation, although the mean time was longer in the control group compared to the rituximab group. There were some benefits in the recovery of graft function (P = 0.026) and improvement of transplant rejection scores at both the 1-month (P = 0.0003) and 6-month (P < 0.0001) follow-up biopsies. (Zarkhin, 2008)

The treatment of AMR in cardiac recipients is largely empirical and includes high-dose corticosteroids, plasmapheresis, IVIG, and rituximab. Data consists primarily of case series and case reports which have documented successful treatment of AMR with rituximab based therapy. (Velez, 2009)

### Induction

A prospective, double-blind, randomized, placebo-controlled study reported results from 140 transplanted individuals. Participants meeting criteria, including PRA less than 50%, were randomized to induction therapy (tacrolimus, mycophenolate mofetil and steroids) plus rituximab versus induction therapy plus placebo. 136 participants fulfilled the study and criteria for analysis. Treatment failure was the primary endpoint with 10 in the rituximab group and 14 in the placebo group (P=0.348). There were 8 rejections in the treatment cohort (11.6%)
versus 12 in the placebo group (17.6%), but this difference was not statistically significant (P=0.317). The authors reported that rejection episodes in the treatment group tended to be less severe. Survival in both groups at 6 months was 98.5% and death censored graft survival 98.5%. (Tyden, 2009)

A three-year follow-up study was conducted. Forty-four (44) of 68 patients were available and analyzed for follow-up in the study group. One graft had been lost in chronic rejection, 8 patients had died and 15 declined participation. Of those 44, it was possible to perform an antibody test to detect donor-specific antibodies in 33. One of those 33 had developed donor-specific antibodies (both class I and class II). In the placebo group, 47 of 68 patients were available for follow-up at 3 years. One graft had been lost in recurrence of the disease and 20 declined participation. Of those 47, testing for donor-specific antibodies was performed in 38, 6 of whom had developed donor-specific antibodies (6 class I and in 3 class II as well). The difference in mortality (8/68 vs. 0/68) was statistically significant (P=0.006). The mortality was attributed to fungal pneumonia (1), pulmonary carcinoma (1), and myocardial infarction/cardiac arrests in 6 cases. The difference in the development of donor-specific antibodies was not significant (P=0.10). In the 3 year follow-up, the main focus was on the development of donor-specific antibodies and the possible implications of that on long-term graft survival. The authors report that they did find a difference in the development of donor-specific antibodies; however, because of the high number of dropouts, this difference did not prove to be significant. There was no difference in the number of graft losses because of late rejection between the groups. (Tyden, 2012)

**Thrombotic thrombocytopenic purpura (TTP)**

There are no randomized trials assessing the use of rituximab with plasma exchange in the management of TTP. Data are limited to a few case reports and case series. A non-randomized, phase 2 trial evaluating the use of rituximab with plasma exchange revealed significant reductions in ADAMTS13 autoantibodies and increases in ADAMTS13 activity, with relapse rates of approximately 10%. (Scully 2011)

**Myasthenia gravis (MG)**

Tanden et al conducted a systematic review of rituximab treatment of myasthenia gravis from 169 patients from case reports and series. This analysis indicated that rituximab is an effective treatment for acetylcholine receptor (AChR) and muscle-specific tyrosine kinase (MuSK), and state typically in most with moderate to severe refractory disease already being treated with several immune-based therapies. AChR are detected in up to 80% of patients with generalized disease and up to 40% of patients with MG who lack a detectable serum ACHR antibodies demonstrate antibodies to MuSK. The study did not allow comment on the optimal rituximab regimen for MG. (Tanden, 2017)

**Systemic Lupus Erymatous**

In one Phase III study that included patients with active proliferative lupus nephritis, the dose used was 1,000 mg administered as an IV infusion on Days 1, 15, 168, and 182. (Pereira, 2011) In a limited number of pediatric patients, alternative dosages based on body surface area (BSA) [dosed in mg/m²] have been evaluated (e.g., 187.5 mg/m² for one dose followed by 375 mg/m² for three weekly doses) and should also be considered for approval. (Rovin, 2012)

**Neuromyelitis Optica**

Common practice is to administer a single course of rituximab IV (375 mg/m²) for 4 weeks or 1,000 mg infused twice within 2 weeks for induction. Protocols for maintenance therapy differ and may be selected based on the circulating B-cell repopulation. (Collongues, 2016)

NMO is an autoimmune inflammatory disease on the central nervous system which is characterized by severe attacks of optic neuritis and longitudinally extensive transverse myelitis. (Kim 2010) Guidelines for the treatment of transverse myelitis note that rituximab should be considered to decrease the number of relapses in patients with transverse myelitis due to NMO. (Kim, 2013)

**Experimental, Investigational, Unproven Uses**

Rituximab has also been studied in a limited number of patients for treating chronic inflammatory demyelinating polyneuropathy. (Querol, 2013, Querol, 2015) At this time there is insufficient evidence to support use of Rituximab in this conditions.
Rituximab has also been studied in a limited number of studies for multiple sclerosis, membranous nephropathy, and IgG4-related disease (common forms or presentation include: Type 1 (IgG4-related) autoimmune pancreatitis, IgG4-related sclerosing cholangitis). (Castillo-Trivino, 2013, Shirani, 2016, Fervenza, 2010, Fervenza, 2019, Khosroshahi, 2012, Khosroshahi 2010) At this time there is insufficient evidence to support use of Rituximab in these conditions.

Rituximab use for pediatric acute-onset neuropsychiatric syndrome (PANS)/ Pediatric autoimmune neuropsychiatric disorder associated with group A streptococci (PANDAS) has not been studied in randomized, controlled trials. Rituximab is mentioned for possible PANS use in the Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part II: Use of Immunomodulatory Therapies (Frankovich, 2017), however is has not been studied in randomized controlled trials.

**Coding/ Billing Information**

**Note:**
1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

**Covered when medically necessary:**

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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<td>J9312</td>
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<tr>
<td>Q5115</td>
<td>Rituximab-abbs (Truxima®)</td>
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**References**

1. AHFS Drug Information 2019 Edition


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