

# Rituximab (Riabni®, Rituxan®, Ruxience®, & Truxima®) (for Pennsylvania Only)

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[Instructions for Use](#)

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## Related Policies

- [Maximum Dosage and Frequency \(for Pennsylvania Only\)](#)
- [Off-Label/Unproven Specialty Drug Treatment](#)
- [Oncology Medication Clinical Coverage \(for Pennsylvania Only\)](#)

## Application

This Medical Benefit Drug Policy only applies to the state of Pennsylvania.

## Coverage Rationale

This policy refers only to the following drug products, rituximab injections for intravenous infusion for non-oncology conditions:

- Riabni® (rituximab-arrx)
- Rituxan® (rituximab)
- Rituxan Hycela® (rituximab and hyaluronidase human)\*
- Ruxience® (rituximab-pvvr)
- Truxima® (rituximab-abbs)
- Any FDA-approved rituximab biosimilar product not listed here\*\*

“Rituximab” will be used to refer to all rituximab products without hyaluronidase.

**\*Rituxan Hycela is unproven and not medically necessary for the treatment of non-oncology indications.** For oncology indications and for Rituxan Hycela (rituximab/hyaluronidase human), refer to the Medical Benefit Drug Policy titled [Oncology Medication Clinical Coverage \(for Pennsylvania Only\)](#) for updated information based upon the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium®(NCCN Compendium®).

## Preferred Product

The preferred product criteria in this section applies to the following states: CO, MD, MI, MN, MS, NE, NJ, NY, OH, PA, RI, TN, TX, and WA. For all other states, coverage will be provided contingent on the coverage criteria in the [Diagnosis-Specific Criteria](#) section.

Truxima (rituximab - abbs) and Ruxience (rituximab - pvvr) are the preferred rituximab products. Coverage will be provided for Truxima and Ruxience contingent on the coverage criteria in the [Diagnosis-Specific Criteria](#) section.

\*\*Any U.S. Food and Drug Administration (FDA) approved and launched rituximab biosimilar product not listed by name in this policy will be considered non-preferred until reviewed by UnitedHealthcare.

Coverage for Rituxan, Riabni (rituximab-arrx), or other rituximab product will be provided contingent on the criteria in this section and the coverage criteria in the [Diagnosis-Specific Criteria](#) section.

### ***Preferred Product Criteria***

Treatment with Rituxan, Riabni, or other rituximab product is medically necessary for the indications specified in the policy when both of the following criteria are met:

- **One** of the following:
  - **Both** of the following:
    - **One** of the following:
      - History of a trial of Truxima resulting in minimal clinical response to therapy and residual disease activity  
**or**
      - History of a trial of Ruxience resulting in minimal clinical response to therapy and residual disease activity  
**and**
    - Physician attests that, in their clinical opinion, the clinical response would be expected to be superior with Rituxan, Riabni, or other rituximab products, than experienced with Truxima or Ruxience
  - or**
  - **Both** of the following:
    - **One** of the following:
      - History of intolerance, contraindication, or adverse event to Truxima; **or**
      - History of intolerance, contraindication, or adverse event to Ruxience  
**and**
    - Physician attests that, in their clinical opinion, the same intolerance, contraindication, or serious adverse event would not be expected to occur with Rituxan, Riabni, or other rituximab products; **and**
- Patient has not had a loss of favorable response after established maintenance therapy with Rituxan, Riabni, or other rituximab products

### ***General Requirements (Applicable to All Medical Necessity Requests)***

- For **initial therapy**, **one** of the following:
  - Prescriber attests dosing is in accordance with the United States Food and Drug Administration (FDA) approved labeling or prescriber attests there is published clinical evidence to support the dosing; **or**
  - For indications without FDA approved dosing, prescriber attests there is published clinical evidence to support the dosing
- For **continuation of therapy**, **both** of the following:
  - Documentation of a positive clinical response; **and**
  - **One** of the following:
    - Prescriber attests dosing is in accordance with the United States Food and Drug Administration (FDA) approved labeling or prescriber attests there is published clinical evidence to support the dosing; **or**
    - For indications without FDA approved dosing, prescriber attests there is published clinical evidence to support the dosing

### ***Diagnosis-Specific Criteria***

The information below indicates additional requirements for those indications having specific medical necessity criteria.

For the coverage criteria below, in absence of specified drug products, the term “Rituximab” will be used in this policy where the coverage criteria apply to all products listed above.

**Rituximab is proven for the treatment of:**

- **Immune thrombocytopenic purpura (ITP)<sup>2,4-16,74,75</sup>**  
**Rituximab is medically necessary for the treatment of immune thrombocytopenic purpura when all of the following criteria are met:**

For **initial therapy**, **all** of the following:

- Diagnosis of immune thrombocytopenic purpura (ITP); **and**
- Documented platelet count < 30 x 10<sup>9</sup>/L; **and**
- History of failure, contraindication, or intolerance to **one** of the following:
  - Anti-D immunoglobulin
  - Corticosteroids
  - Immune globulin
  - Thrombopoietin receptor agonist (TPO-RA) [e.g., Promacta (eltrombopag), Nplate (romiplostim)]

- Splenectomy  
**and**
- Authorization will be for no more than 12 months

For **continuation of therapy**:

- Authorization will be for no more than 12 months

- **Pemphigus vulgaris**<sup>1,3,17-26</sup>

**Rituximab is medically necessary for the treatment of pemphigus vulgaris when all of the following criteria are met:**

For **initial therapy**, **all** of the following:

- Diagnosis of moderate to severe pemphigus vulgaris; **and**
- Initial authorization will be for no more than 12 months

For **continuation of therapy**:

- Reauthorization will be for no more than 12 months

- **Wegener's granulomatosis or microscopic polyangiitis (both ANCA-associated vasculidities)**<sup>1,28-32,75</sup>

**Rituximab is medically necessary for the treatment of Wegener's granulomatosis or microscopic polyangiitis (both ANCA-associated vasculidities) when all of the following criteria are met:**

For **initial therapy**, **all** of the following:

- Diagnosis of Wegener's granulomatosis or microscopic polyangiitis; **and**
- **One** of the following:
  - Patient is receiving concurrent therapy with glucocorticoids
  - History of contraindication or intolerance to glucocorticoids**and**
- Initial authorization will be for no more than 12 months

For **continuation of therapy**:

- Reauthorization will be for no more than 12 months

- **Autoimmune hemolytic anemia, including chronic cold agglutinin disease**<sup>9,33-50,101-2</sup>

**Rituximab is medically necessary for the treatment of autoimmune hemolytic anemia when all of the following criteria are met:**

For **initial therapy**, **both** of the following:

- Diagnosis of autoimmune hemolytic anemia; **and**
- Initial authorization will be for no more than 12 months

For **continuation of therapy**:

- Reauthorization will be for no more than 12 months

- **Rheumatoid arthritis**<sup>1,75,77</sup>

**Rituximab is medically necessary for the treatment of rheumatoid arthritis when all of the following criteria are met:**

For **initial therapy**, **all** of the following:

- Moderate to severe disease activity [e.g., swollen, tender joints with limited range of motion]; **and**
- **One** of the following:
  - Patient is receiving concurrent therapy with methotrexate
  - History of contraindication or intolerance to methotrexate**and**
- History of failure, contraindication, or intolerance to at least **one** tumor necrosis factor (TNF) inhibitors [e.g., adalimumab, Enbrel (etanercept), infliximab (Remicade)]; **and**
- Patient is not receiving rituximab in combination with a targeted immunomodulator. [e.g., adalimumab, Enbrel (etanercept), Cimzia (certolizumab), Simponi (golimumab), Orencia (abatacept), Xeljanz (tofacitinib), Olumiant (baricitinib), Rinvoq (upadacitinib)]; **and**
- Initial authorization will be for no more than 12 months

For **continuation of therapy**, **all** of the following:

- Reauthorization will be for no more than 12 months

- **Post-transplant B-lymphoproliferative disorder (PTLD)<sup>78</sup>**  
**Rituximab is medically necessary for the treatment of post-transplant B-lymphoproliferative disorder when all of the following criteria are met:**  
For **initial therapy**, **both** of the following:
  - Diagnosis of PTLD; **and**
  - Initial authorization will be for no more than 12 months
For **continuation of therapy**:
  - Reauthorization will be for no more than 12 months
  
- **Neuromyelitis optica<sup>32,53,77,79,94-95</sup>**  
**Rituximab is medically necessary for the treatment of neuromyelitis optica when all of the following criteria are met:**  
For **initial therapy**, **all** of the following:
  - Diagnosis of neuromyelitis optica spectrum disorder (NMOSD) by a neurologist confirming all of the following:
    - Serologic testing for anti- aquaporin - 4 immunoglobulin G (AQP4-IgG)/NMO-IgG antibodies has been performed; **and**
    - Past medical history of (if AQP4-IgG/NMO-IgG positive, **one** of the following; if negative, **two** of the following):<sup>25</sup>
      - Optic neuritis
      - Acute myelitis
      - Area postrema syndrome: Episode of otherwise unexplained hiccups or nausea and vomiting
      - Acute brainstem syndrome
      - Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
      - Symptomatic cerebral syndrome with NMOSD-typical brain lesions
      - Diagnosis of multiple sclerosis or other diagnoses have been ruled out
  - and**
  - Prescribed by or in consultation with a neurologist; **and**
  - Patient is **not** receiving rituximab in combination with **any** of the following:
    - Disease modifying therapies for the treatment of multiple sclerosis [e.g., Gilenya (fingolimod), Tecfidera (dimethyl fumarate), Ocrevus (ocrelizumab), etc.]
    - Anti-IL6 therapy [e.g., Actemra (tocilizumab), Kevzara (sarilumab)]
    - Complement inhibitors [e.g., Soliris (eculizumab), Ultomiris (ravulizumab)]
  - and**
  - Initial authorization will be for no more than 12 months
For **continuation of therapy**, **both** of the following:
  - Patient is **not** receiving rituximab in combination with **any** of the following:
    - Disease modifying therapies for the treatment of multiple sclerosis [e.g., Gilenya (fingolimod), Tecfidera (dimethyl fumarate), Ocrevus (ocrelizumab), etc.]
    - Anti-IL6 therapy [e.g., Actemra (tocilizumab), Kevzara (sarilumab)]
    - Complement inhibitors [e.g., Soliris (eculizumab), Ultomiris (ravulizumab)]
  - and**
  - Reauthorization will be for no more than 12 months
  
- **Immunotherapy-related encephalitis<sup>108</sup>**  
**Rituximab is medically necessary for the treatment of immunotherapy-related encephalitis when all of the following criteria are met:**  
For **initial therapy**, **all** of the following:
  - Diagnosis of immunotherapy-related encephalitis; **and**
  - Recent immunotherapy treatment with a checkpoint inhibitor [e.g., Keytruda (pembrolizumab), Opdivo (nivolumab), Tecentriq (atezolizumab)]; **and**
  - **One** of the following:
    - Patient has had limited or no improvement after treatment with glucocorticoids for a minimum of 7 days; **or**
    - History of contraindication or intolerance to glucocorticoids; **or**
    - **Both** of the following:
      - Patient is positive for autoimmune encephalopathy antibody; **and**
      - Infectious causes (e.g., viral) of encephalitis have been ruled out
  - and**
  - Authorization will be for no more than 12 months

For **continuation of therapy**:

- Authorization will be for no more than 12 months

- **Thrombotic thrombocytopenic purpura (TTP)**<sup>110-112</sup>

**Rituximab is medically necessary for acute thrombotic thrombocytopenic purpura when all of the following criteria are met:**

For **initial therapy**, **all** of the following:

- Diagnosis of thrombotic thrombocytopenic purpura; **and**
- Used in combination with plasma exchange therapy; **and**
- **One** of the following:
  - Patient is receiving concurrent therapy with glucocorticoids
  - History of contraindication or intolerance to glucocorticoids**and**
- Authorization will be for no more than 12 months

For **continuation of therapy**:

- Authorization will be for no more than 12 months

- **Multiple sclerosis (MS)**<sup>69,70,113-116</sup>

**Rituximab is medically necessary for multiple sclerosis when all of the following criteria are met:**

For **initial therapy**, **all** of the following:

- **One** of the following:
  - Diagnosis of primary progressive multiple sclerosis (PPMS)
  - Diagnosis of relapsing forms of MS (e.g., relapsing-remitting MS, secondary-progressive MS with relapses, progressive-relapsing MS with relapses)**and**
- Patient is **not** receiving rituximab in combination with **any** of the following:
  - Disease modifying therapy (e.g., interferon beta preparations, dimethyl fumarate, glatiramer acetate, natalizumab, fingolimod, cladribine, siponimod, or teriflunomide)
  - B cell targeted therapy (e.g., ocrelizumab, belimumab, ofatumumab)
  - Lymphocyte trafficking blockers (e.g., alemtuzumab, mitoxantrone)**and**
- Initial authorization will be for no more than 12 months

For **continuation of therapy**, **all** of the following:

- Patient is **not** receiving rituximab in combination with **any** of the following:
  - Disease modifying therapy (e.g., interferon beta preparations, dimethyl fumarate, glatiramer acetate, natalizumab, fingolimod, cladribine, siponimod, or teriflunomide)
  - B cell targeted therapy (e.g., ocrelizumab, belimumab, ofatumumab)
  - Lymphocyte trafficking blockers (e.g., alemtuzumab, mitoxantrone)**and**
- Reauthorization will be for no more than 12 months

- **Immunoglobulin G4-related disease (IgG4-RD)**<sup>115-118</sup>

**Rituximab is medically necessary for the treatment of Immunoglobulin G4-related disease when all of the following criteria are met:**

For **initial therapy**, **all** of the following:

- Diagnosis of Immunoglobulin G4-related disease (IgG4-RD); **and**
- Confirmation of IgG4-RD by a positive assessment using the [ACR/EULAR classification criteria](#), demonstrated by **all** of the following:
  - Involvement of at least 1 or more organ(s) in a manner consistent with IgG4-RD; **and**
  - Exclusion criteria is negative and consistent with an IgG4-RD diagnosis (e.g., clinical findings, serologic results, radiology assessments, pathology interpretations); **and**
  - Inclusion criteria is positive and signifies a diagnosis of IgG4-RD (e.g., clinical findings, serologic results, radiology assessments, pathology interpretations)**and**
- Prescribed by, or in consultation with, a specialist with expertise in the treatment of IgG4-RD; **and**
- Patient is **not** receiving rituximab in combination with a disease modifying therapy for the treatment of IgG4-related disease [e.g., Uplizna (inebilizumab-cdon)]; **and**
- Initial authorization will be for no more than 12 months

For **continuation of therapy**, all of the following:

- Documentation of positive clinical response; **and**
- Prescribed by, or in consultation with, a specialist with expertise in the treatment of IgG4-RD; **and**
- Patient is **not** receiving rituximab in combination with a disease modifying therapy for the treatment of IgG4-related disease [e.g., Uplizna (inebilizumab-cdon)]; **and**
- Reauthorization will be for no more than 12 months

**Rituximab is unproven and not medically necessary for the treatment of:**

- Anti-GM1 antibody-related neuropathies
- Pure red cell aplasia
- Acquired factor VIII inhibitors
- Polyneuropathy associated with anti-MAG antibodies
- Reduction of anti - HLA antibodies in patients awaiting renal transplant

While a beneficial effect of rituximab has been reported in some of these conditions, none of them have shown positive results in large, controlled clinical trials.

**\*Rituxan Hycela is unproven and not medically necessary for the treatment of non-oncology indications.**

For oncology indications and for Rituxan Hycela (rituximab/hyaluronidase human), please refer to the Medical Benefit Drug Policy titled [Oncology Medication Clinical Coverage \(for Pennsylvania Only\)](#) for updated information based upon the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium®(NCCN Compendium®).

## Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J9311	Injection, rituximab 10 mg and hyaluronidase
J9312	Injection, rituximab, 10 mg
Q5115	Injection, rituximab-abbs, biosimilar, (Truxima), 10 mg
Q5119	Injection, rituximab-pvvr, biosimilar, (Ruxience), 10 mg
Q5123	Injection, rituximab-arxx, biosimilar, (Riabni), 10 mg

Diagnosis Code	Description
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)
D59.0	Drug-induced autoimmune hemolytic anemia
D59.10	Autoimmune hemolytic anemia, unspecified
D59.11	Warm autoimmune hemolytic anemia
D59.12	Cold autoimmune hemolytic anemia
D59.13	Mixed type autoimmune hemolytic anemia
D59.19	Other autoimmune hemolytic anemia
D69.3	Immune thrombocytopenic purpura
D89.84	IgG4-related disease
G04.81	Other encephalitis and encephalomyelitis
G35.A	Relapsing-remitting multiple sclerosis
G35.B0	Primary progressive multiple sclerosis, unspecified
G35.B1	Active primary progressive multiple sclerosis
G35.B2	Non-active primary progressive multiple sclerosis
G35.C0	Secondary progressive multiple sclerosis, unspecified

Diagnosis Code	Description
G35.C1	Active secondary progressive multiple sclerosis
G35.C2	Non-active secondary progressive multiple sclerosis
G35.D	Multiple sclerosis, unspecified
G97.82	Other post-procedural complications and disorders of nervous system
G36.0	Neuromyelitis optica
L10.0	Pemphigus vulgaris
L10.1	Pemphigus vegetans
L10.2	Pemphigus foliaceus
L10.3	Brazilian pemphigus (fogo selvage)
L10.4	Pemphigus erythematosus
L10.5	Drug-induced pemphigus
L10.81	Paraneoplastic pemphigus
L10.89	Other pemphigus
L10.9	Pemphigus, unspecified
L12.0	Bullous pemphigoid
L12.1	Cicatricial pemphigoid
L12.8	Other pemphigoid
L12.9	Pemphigoid, unspecified
L13.8	Other specified bullous disorders
L14	Bullous disorders in diseases classified elsewhere
M05.00	Felty's syndrome, unspecified site
M05.011	Felty's syndrome, right shoulder
M05.012	Felty's syndrome, left shoulder
M05.019	Felty's syndrome, unspecified shoulder
M05.021	Felty's syndrome, right elbow
M05.022	Felty's syndrome, left elbow
M05.029	Felty's syndrome, unspecified elbow
M05.031	Felty's syndrome, right wrist
M05.032	Felty's syndrome, left wrist
M05.039	Felty's syndrome, unspecified wrist
M05.041	Felty's syndrome, right hand
M05.042	Felty's syndrome, left hand
M05.049	Felty's syndrome, unspecified hand
M05.051	Felty's syndrome, right hip
M05.052	Felty's syndrome, left hip
M05.059	Felty's syndrome, unspecified hip
M05.061	Felty's syndrome, right knee
M05.062	Felty's syndrome, left knee
M05.069	Felty's syndrome, unspecified knee
M05.071	Felty's syndrome, right ankle and foot
M05.072	Felty's syndrome, left ankle and foot
M05.079	Felty's syndrome, unspecified ankle and foot
M05.09	Felty's syndrome, multiple sites
M05.20	Rheumatoid vasculitis with rheumatoid arthritis of unspecified site
M05.211	Rheumatoid vasculitis with rheumatoid arthritis of right shoulder

Diagnosis Code	Description
M05.212	Rheumatoid vasculitis with rheumatoid arthritis of left shoulder
M05.219	Rheumatoid vasculitis with rheumatoid arthritis of unspecified shoulder
M05.221	Rheumatoid vasculitis with rheumatoid arthritis of right elbow
M05.222	Rheumatoid vasculitis with rheumatoid arthritis of left elbow
M05.229	Rheumatoid vasculitis with rheumatoid arthritis of unspecified elbow
M05.231	Rheumatoid vasculitis with rheumatoid arthritis of right wrist
M05.232	Rheumatoid vasculitis with rheumatoid arthritis of left wrist
M05.239	Rheumatoid vasculitis with rheumatoid arthritis of unspecified wrist
M05.241	Rheumatoid vasculitis with rheumatoid arthritis of right hand
M05.242	Rheumatoid vasculitis with rheumatoid arthritis of left hand
M05.249	Rheumatoid vasculitis with rheumatoid arthritis of unspecified hand
M05.251	Rheumatoid vasculitis with rheumatoid arthritis of right hip
M05.252	Rheumatoid vasculitis with rheumatoid arthritis of left hip
M05.259	Rheumatoid vasculitis with rheumatoid arthritis of unspecified hip
M05.261	Rheumatoid vasculitis with rheumatoid arthritis of right knee
M05.262	Rheumatoid vasculitis with rheumatoid arthritis of left knee
M05.269	Rheumatoid vasculitis with rheumatoid arthritis of unspecified knee
M05.271	Rheumatoid vasculitis with rheumatoid arthritis of right ankle and foot
M05.272	Rheumatoid vasculitis with rheumatoid arthritis of left ankle and foot
M05.279	Rheumatoid vasculitis with rheumatoid arthritis of unspecified ankle and foot
M05.29	Rheumatoid vasculitis with rheumatoid arthritis of multiple sites
M05.30	Rheumatoid heart disease with rheumatoid arthritis of unspecified site
M05.311	Rheumatoid heart disease with rheumatoid arthritis of right shoulder
M05.312	Rheumatoid heart disease with rheumatoid arthritis of left shoulder
M05.319	Rheumatoid heart disease with rheumatoid arthritis of unspecified shoulder
M05.321	Rheumatoid heart disease with rheumatoid arthritis of right elbow
M05.322	Rheumatoid heart disease with rheumatoid arthritis of left elbow
M05.329	Rheumatoid heart disease with rheumatoid arthritis of unspecified elbow
M05.331	Rheumatoid heart disease with rheumatoid arthritis of right wrist
M05.332	Rheumatoid heart disease with rheumatoid arthritis of left wrist
M05.339	Rheumatoid heart disease with rheumatoid arthritis of unspecified wrist
M05.341	Rheumatoid heart disease with rheumatoid arthritis of right hand
M05.342	Rheumatoid heart disease with rheumatoid arthritis of left hand
M05.349	Rheumatoid heart disease with rheumatoid arthritis of unspecified hand
M05.351	Rheumatoid heart disease with rheumatoid arthritis of right hip
M05.352	Rheumatoid heart disease with rheumatoid arthritis of left hip
M05.359	Rheumatoid heart disease with rheumatoid arthritis of unspecified hip
M05.361	Rheumatoid heart disease with rheumatoid arthritis of right knee
M05.362	Rheumatoid heart disease with rheumatoid arthritis of left knee
M05.369	Rheumatoid heart disease with rheumatoid arthritis of unspecified knee
M05.371	Rheumatoid heart disease with rheumatoid arthritis of right ankle and foot
M05.372	Rheumatoid heart disease with rheumatoid arthritis of left ankle and foot
M05.379	Rheumatoid heart disease with rheumatoid arthritis of unspecified ankle and foot
M05.39	Rheumatoid heart disease with rheumatoid arthritis of multiple sites
M05.40	Rheumatoid myopathy with rheumatoid arthritis of unspecified site

Diagnosis Code	Description
M05.411	Rheumatoid myopathy with rheumatoid arthritis of right shoulder
M05.412	Rheumatoid myopathy with rheumatoid arthritis of left shoulder
M05.419	Rheumatoid myopathy with rheumatoid arthritis of unspecified shoulder
M05.421	Rheumatoid myopathy with rheumatoid arthritis of right elbow
M05.422	Rheumatoid myopathy with rheumatoid arthritis of left elbow
M05.429	Rheumatoid myopathy with rheumatoid arthritis of unspecified elbow
M05.431	Rheumatoid myopathy with rheumatoid arthritis of right wrist
M05.432	Rheumatoid myopathy with rheumatoid arthritis of left wrist
M05.439	Rheumatoid myopathy with rheumatoid arthritis of unspecified wrist
M05.441	Rheumatoid myopathy with rheumatoid arthritis of right hand
M05.442	Rheumatoid myopathy with rheumatoid arthritis of left hand
M05.449	Rheumatoid myopathy with rheumatoid arthritis of unspecified hand
M05.451	Rheumatoid myopathy with rheumatoid arthritis of right hip
M05.452	Rheumatoid myopathy with rheumatoid arthritis of left hip
M05.459	Rheumatoid myopathy with rheumatoid arthritis of unspecified hip
M05.461	Rheumatoid myopathy with rheumatoid arthritis of right knee
M05.462	Rheumatoid myopathy with rheumatoid arthritis of left knee
M05.469	Rheumatoid myopathy with rheumatoid arthritis of unspecified knee
M05.471	Rheumatoid myopathy with rheumatoid arthritis of right ankle and foot
M05.472	Rheumatoid myopathy with rheumatoid arthritis of left ankle and foot
M05.479	Rheumatoid myopathy with rheumatoid arthritis of unspecified ankle and foot
M05.49	Rheumatoid myopathy with rheumatoid arthritis of multiple sites
M05.50	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified site
M05.511	Rheumatoid polyneuropathy with rheumatoid arthritis of right shoulder
M05.512	Rheumatoid polyneuropathy with rheumatoid arthritis of left shoulder
M05.519	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified shoulder
M05.521	Rheumatoid polyneuropathy with rheumatoid arthritis of right elbow
M05.522	Rheumatoid polyneuropathy with rheumatoid arthritis of left elbow
M05.529	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified elbow
M05.531	Rheumatoid polyneuropathy with rheumatoid arthritis of right wrist
M05.532	Rheumatoid polyneuropathy with rheumatoid arthritis of left wrist
M05.539	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified wrist
M05.541	Rheumatoid polyneuropathy with rheumatoid arthritis of right hand
M05.542	Rheumatoid polyneuropathy with rheumatoid arthritis of left hand
M05.549	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hand
M05.551	Rheumatoid polyneuropathy with rheumatoid arthritis of right hip
M05.552	Rheumatoid polyneuropathy with rheumatoid arthritis of left hip
M05.559	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hip
M05.561	Rheumatoid polyneuropathy with rheumatoid arthritis of right knee
M05.562	Rheumatoid polyneuropathy with rheumatoid arthritis of left knee
M05.569	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified knee
M05.571	Rheumatoid polyneuropathy with rheumatoid arthritis of right ankle and foot
M05.572	Rheumatoid polyneuropathy with rheumatoid arthritis of left ankle and foot
M05.579	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified ankle and foot
M05.59	Rheumatoid polyneuropathy with rheumatoid arthritis of multiple sites

Diagnosis Code	Description
M05.60	Rheumatoid arthritis of unspecified site with involvement of other organs and systems
M05.611	Rheumatoid arthritis of right shoulder with involvement of other organs and systems
M05.612	Rheumatoid arthritis of left shoulder with involvement of other organs and systems
M05.619	Rheumatoid arthritis of unspecified shoulder with involvement of other organs and systems
M05.621	Rheumatoid arthritis of right elbow with involvement of other organs and systems
M05.622	Rheumatoid arthritis of left elbow with involvement of other organs and systems
M05.629	Rheumatoid arthritis of unspecified elbow with involvement of other organs and systems
M05.631	Rheumatoid arthritis of right wrist with involvement of other organs and systems
M05.632	Rheumatoid arthritis of left wrist with involvement of other organs and systems
M05.639	Rheumatoid arthritis of unspecified wrist with involvement of other organs and systems
M05.641	Rheumatoid arthritis of right hand with involvement of other organs and systems
M05.642	Rheumatoid arthritis of left hand with involvement of other organs and systems
M05.649	Rheumatoid arthritis of unspecified hand with involvement of other organs and systems
M05.651	Rheumatoid arthritis of right hip with involvement of other organs and systems
M05.652	Rheumatoid arthritis of left hip with involvement of other organs and systems
M05.659	Rheumatoid arthritis of unspecified hip with involvement of other organs and systems
M05.661	Rheumatoid arthritis of right knee with involvement of other organs and systems
M05.662	Rheumatoid arthritis of left knee with involvement of other organs and systems
M05.669	Rheumatoid arthritis of unspecified knee with involvement of other organs and systems
M05.671	Rheumatoid arthritis of right ankle and foot with involvement of other organs and systems
M05.672	Rheumatoid arthritis of left ankle and foot with involvement of other organs and systems
M05.679	Rheumatoid arthritis of unspecified ankle and foot with involvement of other organs and systems
M05.69	Rheumatoid arthritis of multiple sites with involvement of other organs and systems
M05.7A	Rheumatoid arthritis with rheumatoid factor of other specified site without organ or systems involvement
M05.70	Rheumatoid arthritis with rheumatoid factor of unspecified site without organ or systems involvement
M05.711	Rheumatoid arthritis with rheumatoid factor of right shoulder without organ or systems involvement
M05.712	Rheumatoid arthritis with rheumatoid factor of left shoulder without organ or systems involvement
M05.719	Rheumatoid arthritis with rheumatoid factor of unspecified shoulder without organ or systems involvement
M05.721	Rheumatoid arthritis with rheumatoid factor of right elbow without organ or systems involvement
M05.722	Rheumatoid arthritis with rheumatoid factor of left elbow without organ or systems involvement
M05.729	Rheumatoid arthritis with rheumatoid factor of unspecified elbow without organ or systems involvement
M05.731	Rheumatoid arthritis with rheumatoid factor of right wrist without organ or systems involvement
M05.732	Rheumatoid arthritis with rheumatoid factor of left wrist without organ or systems involvement
M05.739	Rheumatoid arthritis with rheumatoid factor of unspecified wrist without organ or systems involvement
M05.741	Rheumatoid arthritis with rheumatoid factor of right hand without organ or systems involvement
M05.742	Rheumatoid arthritis with rheumatoid factor of left hand without organ or systems involvement
M05.749	Rheumatoid arthritis with rheumatoid factor of unspecified hand without organ or systems involvement
M05.751	Rheumatoid arthritis with rheumatoid factor of right hip without organ or systems involvement
M05.752	Rheumatoid arthritis with rheumatoid factor of left hip without organ or systems involvement
M05.759	Rheumatoid arthritis with rheumatoid factor of unspecified hip without organ or systems involvement

Diagnosis Code	Description
M05.761	Rheumatoid arthritis with rheumatoid factor of right knee without organ or systems involvement
M05.762	Rheumatoid arthritis with rheumatoid factor of left knee without organ or systems involvement
M05.769	Rheumatoid arthritis with rheumatoid factor of unspecified knee without organ or systems involvement
M05.771	Rheumatoid arthritis with rheumatoid factor of right ankle and foot without organ or systems involvement
M05.772	Rheumatoid arthritis with rheumatoid factor of left ankle and foot without organ or systems involvement
M05.779	Rheumatoid arthritis with rheumatoid factor of unspecified ankle and foot without organ or systems involvement
M05.79	Rheumatoid arthritis with rheumatoid factor of multiple sites without organ or systems involvement
M05.8A	Other rheumatoid arthritis with rheumatoid factor of other specified site
M05.80	Other rheumatoid arthritis with rheumatoid factor of unspecified site
M05.811	Other rheumatoid arthritis with rheumatoid factor of right shoulder
M05.812	Other rheumatoid arthritis with rheumatoid factor of left shoulder
M05.819	Other rheumatoid arthritis with rheumatoid factor of unspecified shoulder
M05.821	Other rheumatoid arthritis with rheumatoid factor of right elbow
M05.822	Other rheumatoid arthritis with rheumatoid factor of left elbow
M05.829	Other rheumatoid arthritis with rheumatoid factor of unspecified elbow
M05.831	Other rheumatoid arthritis with rheumatoid factor of right wrist
M05.832	Other rheumatoid arthritis with rheumatoid factor of left wrist
M05.839	Other rheumatoid arthritis with rheumatoid factor of unspecified wrist
M05.841	Other rheumatoid arthritis with rheumatoid factor of right hand
M05.842	Other rheumatoid arthritis with rheumatoid factor of left hand
M05.849	Other rheumatoid arthritis with rheumatoid factor of unspecified hand
M05.851	Other rheumatoid arthritis with rheumatoid factor of right hip
M05.852	Other rheumatoid arthritis with rheumatoid factor of left hip
M05.859	Other rheumatoid arthritis with rheumatoid factor of unspecified hip
M05.861	Other rheumatoid arthritis with rheumatoid factor of right knee
M05.862	Other rheumatoid arthritis with rheumatoid factor of left knee
M05.869	Other rheumatoid arthritis with rheumatoid factor of unspecified knee
M05.871	Other rheumatoid arthritis with rheumatoid factor of right ankle and foot
M05.872	Other rheumatoid arthritis with rheumatoid factor of left ankle and foot
M05.879	Other rheumatoid arthritis with rheumatoid factor of unspecified ankle and foot
M05.89	Other rheumatoid arthritis with rheumatoid factor of multiple sites
M05.9	Rheumatoid arthritis with rheumatoid factor, unspecified
M06.0A	Rheumatoid arthritis without rheumatoid factor, other specified site
M06.00	Rheumatoid arthritis without rheumatoid factor, unspecified site
M06.011	Rheumatoid arthritis without rheumatoid factor, right shoulder
M06.012	Rheumatoid arthritis without rheumatoid factor, left shoulder
M06.019	Rheumatoid arthritis without rheumatoid factor, unspecified shoulder
M06.021	Rheumatoid arthritis without rheumatoid factor, right elbow
M06.022	Rheumatoid arthritis without rheumatoid factor, left elbow
M06.029	Rheumatoid arthritis without rheumatoid factor, unspecified elbow
M06.031	Rheumatoid arthritis without rheumatoid factor, right wrist
M06.032	Rheumatoid arthritis without rheumatoid factor, left wrist

Diagnosis Code	Description
M06.039	Rheumatoid arthritis without rheumatoid factor, unspecified wrist
M06.041	Rheumatoid arthritis without rheumatoid factor, right hand
M06.042	Rheumatoid arthritis without rheumatoid factor, left hand
M06.049	Rheumatoid arthritis without rheumatoid factor, unspecified hand
M06.051	Rheumatoid arthritis without rheumatoid factor, right hip
M06.052	Rheumatoid arthritis without rheumatoid factor, left hip
M06.059	Rheumatoid arthritis without rheumatoid factor, unspecified hip
M06.061	Rheumatoid arthritis without rheumatoid factor, right knee
M06.062	Rheumatoid arthritis without rheumatoid factor, left knee
M06.069	Rheumatoid arthritis without rheumatoid factor, unspecified knee
M06.071	Rheumatoid arthritis without rheumatoid factor, right ankle and foot
M06.072	Rheumatoid arthritis without rheumatoid factor, left ankle and foot
M06.079	Rheumatoid arthritis without rheumatoid factor, unspecified ankle and foot
M06.08	Rheumatoid arthritis without rheumatoid factor, vertebrae
M06.09	Rheumatoid arthritis without rheumatoid factor, multiple sites
M06.1	Adult-onset Still's disease
M06.20	Rheumatoid bursitis, unspecified site
M06.211	Rheumatoid bursitis, right shoulder
M06.212	Rheumatoid bursitis, left shoulder
M06.219	Rheumatoid bursitis, unspecified shoulder
M06.221	Rheumatoid bursitis, right elbow
M06.222	Rheumatoid bursitis, left elbow
M06.229	Rheumatoid bursitis, unspecified elbow
M06.231	Rheumatoid bursitis, right wrist
M06.232	Rheumatoid bursitis, left wrist
M06.239	Rheumatoid bursitis, unspecified wrist
M06.241	Rheumatoid bursitis, right hand
M06.242	Rheumatoid bursitis, left hand
M06.249	Rheumatoid bursitis, unspecified hand
M06.251	Rheumatoid bursitis, right hip
M06.252	Rheumatoid bursitis, left hip
M06.259	Rheumatoid bursitis, unspecified hip
M06.261	Rheumatoid bursitis, right knee
M06.262	Rheumatoid bursitis, left knee
M06.269	Rheumatoid bursitis, unspecified knee
M06.271	Rheumatoid bursitis, right ankle and foot
M06.272	Rheumatoid bursitis, left ankle and foot
M06.279	Rheumatoid bursitis, unspecified ankle and foot
M06.28	Rheumatoid bursitis, vertebrae
M06.29	Rheumatoid bursitis, multiple sites
M06.30	Rheumatoid nodule, unspecified site
M06.311	Rheumatoid nodule, right shoulder
M06.312	Rheumatoid nodule, left shoulder
M06.319	Rheumatoid nodule, unspecified shoulder
M06.321	Rheumatoid nodule, right elbow

Diagnosis Code	Description
M06.322	Rheumatoid nodule, left elbow
M06.329	Rheumatoid nodule, unspecified elbow
M06.331	Rheumatoid nodule, right wrist
M06.332	Rheumatoid nodule, left wrist
M06.339	Rheumatoid nodule, unspecified wrist
M06.341	Rheumatoid nodule, right hand
M06.342	Rheumatoid nodule, left hand
M06.349	Rheumatoid nodule, unspecified hand
M06.351	Rheumatoid nodule, right hip
M06.352	Rheumatoid nodule, left hip
M06.359	Rheumatoid nodule, unspecified hip
M06.361	Rheumatoid nodule, right knee
M06.362	Rheumatoid nodule, left knee
M06.369	Rheumatoid nodule, unspecified knee
M06.371	Rheumatoid nodule, right ankle and foot
M06.372	Rheumatoid nodule, left ankle and foot
M06.379	Rheumatoid nodule, unspecified ankle and foot
M06.38	Rheumatoid nodule, vertebrae
M06.39	Rheumatoid nodule, multiple sites
M06.4	Inflammatory polyarthropathy
M06.8A	Other specified rheumatoid arthritis, other specified site
M06.80	Other specified rheumatoid arthritis, unspecified site
M06.811	Other specified rheumatoid arthritis, right shoulder
M06.812	Other specified rheumatoid arthritis, left shoulder
M06.819	Other specified rheumatoid arthritis, unspecified shoulder
M06.821	Other specified rheumatoid arthritis, right elbow
M06.822	Other specified rheumatoid arthritis, left elbow
M06.829	Other specified rheumatoid arthritis, unspecified elbow
M06.831	Other specified rheumatoid arthritis, right wrist
M06.832	Other specified rheumatoid arthritis, left wrist
M06.839	Other specified rheumatoid arthritis, unspecified wrist
M06.841	Other specified rheumatoid arthritis, right hand
M06.842	Other specified rheumatoid arthritis, left hand
M06.849	Other specified rheumatoid arthritis, unspecified hand
M06.851	Other specified rheumatoid arthritis, right hip
M06.852	Other specified rheumatoid arthritis, left hip
M06.859	Other specified rheumatoid arthritis, unspecified hip
M06.861	Other specified rheumatoid arthritis, right knee
M06.862	Other specified rheumatoid arthritis, left knee
M06.869	Other specified rheumatoid arthritis, unspecified knee
M06.871	Other specified rheumatoid arthritis, right ankle and foot
M06.872	Other specified rheumatoid arthritis, left ankle and foot
M06.879	Other specified rheumatoid arthritis, unspecified ankle and foot
M06.88	Other specified rheumatoid arthritis, vertebrae
M06.89	Other specified rheumatoid arthritis, multiple sites

Diagnosis Code	Description
M06.9	Rheumatoid arthritis, unspecified
M30.0	Polyarteritis nodosa
M30.1	Polyarteritis with lung involvement [Churg-Strauss]
M30.2	Juvenile polyarteritis
M30.8	Other conditions related to polyarteritis nodosa
M31.10	Thrombotic microangiopathy, unspecified
M31.11	Hematopoietic stem cell transplantation-associated thrombotic microangiopathy [HSCT-TMA]
M31.19	Other thrombotic microangiopathy
M31.30	Wegener's granulomatosis without renal involvement
M31.31	Wegener's granulomatosis with renal involvement
M31.7	Microscopic polyangiitis
T45.1X5A	Adverse effect of antineoplastic and immunosuppressive drugs, initial encounter
T45.1X5D	Adverse effect of antineoplastic and immunosuppressive drugs, subsequent encounter
T45.1X5S	Adverse effect of antineoplastic and immunosuppressive drugs, sequela
Z92.22	Personal history of monoclonal drug therapy

## Background

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B-lymphocytes. CD20 regulates an early step(s) in the activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion channel. CD20 is not shed from the cell surface and does not internalize upon antibody binding. The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis in vitro.<sup>1</sup>

## Clinical Evidence

### Proven

#### *Immune Thrombocytopenic Purpura (ITP)*

A randomized open label phase 3 trial of newly diagnosed adult immune thrombocytopenia patients (n = 133) was conducted to evaluate treatment with dexamethasone alone or in combination with rituximab.<sup>2</sup> Eligible were patients with platelet counts  $\leq 25 \times 10^9/L$  or  $\leq 50 \times 10^9/L$  with bleeding symptoms. Study participants were randomly assigned to either dexamethasone 40 mg/day for 4 days (n = 71) or in combination with rituximab 375 mg/m<sup>2</sup> weekly for 4 weeks (n = 62). Patients were allowed supplemental dexamethasone every 1 to 4 weeks for up to 6 cycles. The primary end point, sustained response (i.e., platelets  $\geq 50 \times 10^9/L$  with) at 6 months follow-up, was reached in 58% of patients in the rituximab + dexamethasone group versus 37% in the dexamethasone group (p = 0.02). Median time to follow-up was 922 days. Additional findings in the rituximab + dexamethasone group were longer time to relapse (p = 0.03) and longer time to rescue treatment (p = 0.007). A greater incidence of grade 3 to 4 adverse events was reported in the rituximab + dexamethasone group (p = 0.04).

#### *Autoimmune Mucocutaneous Blistering Diseases*

A retrospective cohort study was conducted to assess the clinical response of patients with pemphigus to rituximab using a modified fixed-dose rheumatoid arthritis protocol.<sup>3</sup> Participants included 92 patients (pemphigus vulgaris, n = 84, and pemphigus foliaceus, n = 8) who received rituximab treatment 1 g intravenously on days 1 and 15, followed by 500 mg intravenously if clinically warranted at 6-month intervals or repeated full dosing. The primary outcomes were time to relapse and achievement of a complete response with or without treatment at the end of the study. Median time to relapse after the first treatment cycle was 15 months (95% CI, 10.3 - 19.7). All patients experienced improvement, while no serious infectious adverse events occurred. Complete remission rates with or without adjuvant treatment at final follow-up were 89% [56 patients (61%) were in complete remission without treatment and 26 patients (28%) were in complete remission during adjuvant treatment]. Investigators concluded that the fixed dose, modified rheumatoid arthritis protocol for rituximab was efficacious and well tolerated in patients with pemphigus. Patients who do not achieve remission after 1 cycle or patients who experience relapse benefit from further cycles of rituximab.

## ***Autoimmune Hemolytic Anemia***

The sustained response to low-dose (LD) rituximab in autoimmune hemolytic anemia (AIHA) was evaluated in a study of 32 patients.<sup>28</sup> Study subjects had either warm (W) AIHA (n = 18) or cold hemagglutinin disease (CHD) (n = 14) and received LD rituximab (100 mg fixed dose ×4 weekly infusions) along with a short course of oral prednisone. Complete clinical examination, blood counts, and hemolytic markers were performed at enrollment and at month 6, 12, 24, and 36. Hematological parameters significantly improved at all time points compared to enrollment. The overall response was 90%, 100%, 100%, and 89% and the relapse-free survival 87%, 79%, 68%, and 68% at 6, 12, 24, and 36 months, respectively. Response rates were slightly better in WAIHA than in CHD, and relapse risk was greater in cold than warm forms (HR 2.1, 95% CI 0.6 - 7.9). Four patients were retreated (one patient twice) with all achieving a response, lasting a median of 18 months (range 9 - 30). Treatment was well tolerated without adverse events or infections. Anti - RBC antibody production by MS-DAT significantly decreased over time. In vitro studies showed that rituximab effectively inhibited anti-RBC antibody production at 50 µg/mL, one-sixth of the drug concentration after therapy with standard doses.

The impact of first-line treatment with rituximab was studied in 64 patients with newly diagnosed warm-antibody reactive autoimmune hemolytic anemia (WAIHA).<sup>29</sup> Subjects randomly received either prednisolone and rituximab combined (n = 32) or prednisolone monotherapy (n = 32). After 12 months, a satisfactory response was observed in 75% of the patients treated with rituximab and prednisolone but in a significantly smaller proportion (36%) of those given prednisolone alone (p = 0.003). Relapse-free survival was significantly better after the combined therapy than after prednisolone monotherapy (p = 0.02). After 36 months, about 70% of the patients were still in remission in the rituximab-prednisolone group, whereas only about 45% were still in complete or partial remission in the prednisolone group. There was no significant difference between the two groups regarding adverse reactions to the studied medications. Likewise, serious adverse events were equally distributed, and no allergic reactions to rituximab were recorded. The investigators found that using rituximab and prednisolone combined rather than prednisolone alone as first-line treatment in WAIHA increases both the rate and the duration of the response.

## ***Chronic Cold Agglutinin Disease***

Rituximab was effective in the treatment of primary chronic cold agglutinin disease (CAD), a type of autoimmune hemolytic anemia, in a multicenter, phase 2 clinical trial.<sup>48</sup> Patients (n = 27; mean age, 71 years; range, 51 - 91 years) consisted of 18 men and 9 women; 12 were previously untreated, 10 had received one prior treatment, and 5 had received at least 2 prior treatments. Rituximab was administered at a dose of 375 mg/m<sup>2</sup> IV weekly for 4 consecutive weeks. Retreatment with rituximab was allowed, with the addition of interferon-alpha (IFN), for patients who did not respond within 3 months or who relapsed. Complete response (CR) was defined as the absence of anemia, no signs of hemolysis, no clinical symptoms of CAD, no detectable monoclonal serum protein, and no signs of clonal lymphoproliferation (assessed by bone marrow histology, immunohistochemistry, and flow cytometry). Partial response (PR) included a stable increase in hemoglobin (Hgb) of at least 2 g/dL or to the normal range, a reduction of serum immunoglobulin M (IgM) concentrations by at least 50% of baseline or to the normal range, improvement of clinical symptoms, and transfusion independence. At baseline, bone marrow histology consisted of lymphoplasmacytic lymphoma (n = 15), marginal zone lymphoma (n = 2), small B-cell lymphoma (n = 2), unclassified clonal lymphoproliferation (n = 6), and reactive lymphocytic infiltration/no clonal lymphoproliferative disorder (n = 2). After the first course of rituximab, 1 complete response and 13 partial responses (n = 27) occurred. Treatment with rituximab plus IFN in 2 non - responders produced one PR. Of initial responders, 8 patients relapsed and were retreated with rituximab alone (n = 5; resulting in 3 PR) or rituximab plus IFN (n = 3; resulting in 2 PR). Of patients (n = 2) who were retreated with rituximab alone for a second relapse, both resulted in PR. Of all 37 courses of treatment with rituximab with or without IFN, the overall response rate was 54% (CR, 3%; PR, 51%). Median time to response was 1.5 months (mean, 1.7 months; range, 0.5 - 4 months). The median increase in Hgb in responders was 4 g/dL (mean, 4.1 g/dL; range, 0.7-7.1 g/dL). Increases in Hgb from 2 to 4.3 g/dL occurred in 4 non - responders and improvements in clinical symptoms occurred in 6 of 17 non - responders. Median duration of response was 11 months (mean, 13 months; range, 2 - 42 months), calculated in 17 responders who were observed until relapse or for at least 12 months after they achieved response. The duration of the one CR was 42 months. All patients achieved reduced percentages of CD20 + cells on flow cytometry.

Rituximab was studied in a phase II multicenter trial in 20 patients with CAD.<sup>49</sup> Thirteen patients had idiopathic CAD and seven patients had CAD associated with a malignant B-cell lymphoproliferative disease. Rituximab was given in doses of 375 mg/m<sup>2</sup> at days 1, 8, 15, and 22. Sixteen patients were followed up for at least 48 weeks. Four patients were excluded after 8, 16, 23, and 28 weeks for reasons unrelated to CAD. Nine patients (45%) responded to the treatment, one with complete response (CR), and eight with partial response. Eight patients relapsed, and one patient was still in remission at the end of follow-up. There were no serious rituximab-related side effects. The authors considered the results noteworthy for a disease where conventional treatment regimens have notoriously been futile.

## ***Post-Transplant B-Lymphoproliferative Disorder***

Rituximab monotherapy is recommended as first-line therapy for monomorphic or polymorphic post-transplant lymphoproliferative disorder (PTLD). It is also recommended as second-line therapy for persistent or progressive early lesions or for persistent or progressive monomorphic PTLD if reduction of immunosuppressive was used as first-line therapy. Rituximab monotherapy is also recommended as maintenance therapy for polymorphic PTLD achieving complete response on first-line therapy.<sup>78</sup>

Rituximab is recommended as a component of multiple regimens [e.g., RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)] for concurrent chemoimmunotherapy as first-line therapy for monomorphic or systemic polymorphic PTLD and as second-line therapy for persistent or progressive monomorphic or polymorphic PTLD.<sup>78</sup>

Rituximab is recommended as sequential chemoimmunotherapy as a single agent followed by CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen as first-line therapy for monomorphic or systemic polymorphic PTLD and as second-line therapy for persistent or progressive monomorphic or polymorphic PTLD.<sup>78</sup>

## ***Neuromyelitis Optica***

In their review of relapse therapy and intermittent long-term therapy, the Neuromyelitis Optica Study Group (NEMOS) recommends B - cell depletion with rituximab at either two 1 g infusions at an interval of 2 weeks or four weekly 375 mg/m<sup>2</sup> infusions.<sup>32</sup> Increasing evidence shows that incomplete B-cell depletion and/or B-cell repopulation is associated with relapse risk in neuromyelitis optica. Because most patients remain B-cell deficient for 6 months after rituximab treatment, re-dosing every 6 months is considered to be an adequate retreatment frequency.

Kim et al. reported their findings from a retrospective case series of 30 patients with relapsing NMO or NMO spectrum disorder who received rituximab for a median of 60 months.<sup>53</sup> After induction therapy, a single infusion of rituximab (375 mg/m<sup>2</sup>) as maintenance therapy was administered whenever the frequency of reemerging CD27 + memory B cells in peripheral blood mononuclear cells as measured with flow cytometry, exceeded 0.05% in the first 2 years and 0.1% thereafter. The main outcome measures were annualized relapse rate (ARR), disability (Expanded Disability Status Scale score), change in anti - aquaporin 4 antibody, and safety of rituximab treatment. Of 30 patients, 26 (87%) exhibited a marked reduction in ARR over 5 years [mean (SD) pretreatment versus posttreatment ARR, 2.4 (1.5) versus 0.3 (1.0)]. Eighteen patients (60%) became relapse free after rituximab treatment. In 28 patients (93%), the disability was either improved or stabilized after rituximab treatment. No serious adverse events leading to discontinuation were observed during follow-up. The investigators concluded that repeated treatment with rituximab in patients with NMOSD over a 5-period, using an individualized dosing schedule according to the frequency of reemerging CD27 + memory B cells, leads to a sustained clinical response with no new adverse events.

A retrospective, multicenter analysis of relapses in 90 patients with NMO and NMO spectrum disorder was conducted to compare the relapse and treatment failure rates among patients receiving the 3 most common forms of immunosuppression for NMO: azathioprine, mycophenolate mofetil, and rituximab.<sup>77</sup> Rituximab reduced the relapse rate up to 88.2%, with 2 in 3 patients achieving complete remission. Mycophenolate reduced the relapse rate by up to 87.4%, with a 36% failure rate. Azathioprine reduced the relapse rate by 72.1% but had a 53% failure rate despite concurrent use of prednisone. Based up these findings, the investigators concluded that initial treatment with rituximab, mycophenolate, and, to a lesser degree, azathioprine significantly reduces relapse rates in NMO and NMO spectrum disorder patients. Patients for whom initial treatment fails often achieve remission when treatment is switched from one to another of these drugs.

In a 2012 review of evidence by Sato et al., the investigators identified six open label studies involving a total of 76 patients who experienced positive results from rituximab therapy for NMO.<sup>79</sup> Based upon these findings, they assigned a Grade 1C,III rating (strong recommendation based upon observational studies or case series) for the treatment of NMO with rituximab.

A prospective open-label study was conducted to evaluate the efficacy and safety of repeated rituximab treatment over 24 months in patients with relapsing neuromyelitis optica (NMO).<sup>94</sup> Thirty patients with relapsing NMO or NMO spectrum disorder received a treatment protocol of rituximab induction therapy (375 mg/m<sup>2</sup> once weekly for 4 weeks or 1,000 mg infused twice, with a 2-week interval between the infusions) followed by maintenance therapy. The maintenance therapy consisted of repeated treatment with rituximab (375 mg/m<sup>2</sup>, once) whenever the frequency of reemerging CD27 + memory B - cells was greater than 0.05% in peripheral blood mononuclear cells by flow cytometric analysis. The main outcome measures were annualized relapse rate, disability (Expanded Disability Status Scale score), anti - aquaporin 4 antibody level, and safety of rituximab treatment. Of 30 patients, 28 showed a marked reduction in relapse rate while

taking rituximab over 24 months. The relapse rate was reduced significantly, by 88%, and 70% of patients became relapse-free over 24 months. Disability either improved or stabilized in 97% of patients. Anti - aquaporin 4 antibody levels declined significantly following treatment with rituximab, consistent with the clinical response and the effect on CD27 + memory B-cells. Repeated treatment with rituximab was generally well tolerated, and no clinically relevant adverse event leading to discontinuation of treatment was observed. The investigators concluded that repeated treatment with rituximab appeared to produce consistent and sustained efficacy over 24 months with good tolerability in patients with NMO.

### ***Thrombotic Thrombocytopenic Purpura***

In an open label, phase II, prospective study, Froissart A et al. assessed the efficacy and safety of rituximab in adults with poor responses to standard treatment for severe autoimmune thrombotic thrombocytopenic purpura.<sup>111</sup> The authors compared outcomes of survivors to outcomes of historical survivors who had received therapeutic plasma exchange alone or with vincristine. Participants included 22 adults with either no response or a disease exacerbation when treated with intensive therapeutic plasma exchange as well as rituximab therapy consisting of four infusions over 15 days. The authors report that one patient who had received rituximab died. In the rituximab treatment group, the time to a durable remission was significantly shortened ( $p = .03$ ), however plasma volume required to achieve a durable remission was not significantly different in the treatment group compared to the control group. Platelet count recovery occurred within 35 days in all survivors in the treatment group, compared to only 78% of the historical controls ( $p < .02$ ). Of the rituximab-treated patients, none had a relapse within the first year but three experienced relapses later. The authors conclude that adults with severe thrombocytopenic purpura who responded poorly to therapeutic plasma exchange and who were treated with rituximab had shorter overall treatment duration and reduced 1-yr relapses than historical controls.

Scully M. et al evaluated the safety and efficacy of weekly rituximab given within 3 days of acute TTP admission, in combination with plasma exchange (PEX) and steroids.<sup>112</sup> Historical controls ( $n = 40$ ) who had not received rituximab were used as a comparator group. For the treatment group receiving rituximab, 15 of 40 required ICU admission. Prior to the second rituximab infusion, 68% of cases had a platelet count  $> 50 \times 10^9/L$  and 38%  $> 150 \times 10^9/L$ . For non-ICU patients receiving rituximab, inpatient stay was reduced by 7 days compared to historical controls ( $p = .04$ ). Compared to historical controls, 10% of trial cases relapsed, median, 27 months (17-31 months) vs. 57% in historical controls, median 18 months (3-60 months;  $p = .0011$ ). For patients receiving rituximab, there were no major infections or serious adverse events reported. In this trial, for patients who received rituximab, inpatient stay and relapse were significantly reduced. The authors conclude that rituximab appears to be a safe and effective therapy for TTP, and that rituximab should be considered in conjunction with standard therapy on acute presentation of TTP. This study was registered at <http://www.clinicaltrials.gov> as NCT009-3713.

### ***Multiple Sclerosis***

Hauser et al conducted a phase 2, double-blind, 48 - week trial which included 104 patients with relapsing-remitting multiple sclerosis who were assigned to receive 1,000 mg of intravenous rituximab or placebo on days 1 and 15.<sup>69</sup> The primary end point was the total count of gadolinium-enhancing lesions detected on magnetic resonance imaging scans of the brain at weeks 12, 16, 20, and 24. Clinical outcomes included safety, the proportion of patients who had relapses, and the annualized rate of relapse. When compared with patients who received placebo, patients treated with rituximab had reduced counts of total gadolinium - enhancing lesions at weeks 12, 16, 20, and 24 ( $p < 0.001$ ) and as well as reduced counts of total new gadolinium-enhancing lesions over the same period ( $p < 0.001$ ); these results were sustained for 48 weeks ( $p < 0.001$ ). As compared with patients in the placebo group, the proportion of patients in the rituximab group with relapses was significantly reduced at week 24 (14.5% vs. 34.3%,  $p = 0.02$ ) and week 48 (20.3% vs. 40.0%,  $p = 0.04$ ). The authors conclude that single course of rituximab reduced inflammatory brain lesions and clinical relapses for 48 weeks. [ClinicalTrials.gov number, NCT00097188 (ClinicalTrials.gov)].

### ***Immunoglobulin G4-Related Disease (IgG4-RD)***

Rituximab demonstrated efficacy in IgG4-related disease (IgG4-RD) in retrospective nationwide study in France for both an induction and maintenance treatment. Clinical response was noted in 29 of 31 (93.5%) symptomatic patients. Glucocorticoids withdrawal was achieved in 17 (51.5%) patients. Additionally, during a mean follow-up of  $24.8 \pm 21$  months, 13 of 31 (41.9%) responder patients relapsed after a mean delay of  $19 \pm 11$  months after discontinuing treatment with rituximab. Active disease, as defined by an IgG4-RD Responder Index  $> 9$  before initiating rituximab, was significantly associated with relapse (HR = 3.68, 95% CI: 1.1, 12.6) ( $p = 0.04$ ), whereas maintenance therapy with systematic (i.e., before occurrence of a relapse) rituximab retreatment was associated with longer relapse-free survival (41 versus 21 months;  $p = 0.02$ ). In a different open-label trial, 30 patients with IgG4-RD were treated with two doses of rituximab and demonstrated a disease response in 97 percent of the patients. Forty seven percent of patients (14 patients) remained at complete remission at 6 months and 40 percent (12 patients) remained at complete remission at 12 months. In a meta-analysis examining efficacy and safety of rituximab in IgG4-RD with pancreato-biliary manifestations, the pooled rate of complete response at six months was 88.9 percent (95% CI 80.5-93.9) and the relapse rate was 21 percent (95% CI 10.5-

40.3). Moreover, rituximab is cited as a grade 2A recommendation in a European Guideline on IgG4-related digestive disease – UEG and SGF evidence-based recommendations, published in 2020, as an appropriate consideration if patients are resistant or intolerant to high-dose glucocorticoids to maintain remission or have failed to respond to immunosuppressive therapies. The guideline has the following comments: “There is a strong pathophysiological rationale for rituximab use in IgG4-related disease, allowing depletion of the CD20 + B-cell precursors of disease-specific clonal plasma blasts. Depletion of B cells by rituximab has been demonstrated to be highly effective at inducing and maintaining remission. Apart from glucocorticoids, rituximab is the only drug that has been shown to induce remission of IgG4-related disease. Rituximab presents several advantages, such as a glucocorticoid-sparing effect, existing data on remission induction, and (possibly) better safety profile than glucocorticoids or immunosuppressants.”

## **Unproven**

### ***Miscellaneous***

Rituximab has been used in the treatment of other conditions. These include anti-GM1 antibody-related neuropathies,<sup>72-73</sup> pure red cell aplasia,<sup>81-82</sup> acquired factor VIII inhibitors,<sup>83-84</sup> polyneuropathy associated with anti-MAG antibodies,<sup>85,101-2,104</sup> chronic graft-versus-host disease<sup>27,50,51,76,89-92,106</sup> reduction of anti-HLA antibodies in patients awaiting renal transplant,<sup>93</sup> and dermatomyositis and polymyositis.<sup>96-99</sup> While a beneficial effect of rituximab has been reported in each of these conditions, none of these conditions has been studied in large, controlled clinical trials.

## **Technology Assessments**

### ***Rheumatoid Arthritis***

A 2015 Cochrane review was published reviewing the effect of rituximab in patients with rheumatoid arthritis.<sup>107</sup> The review evaluated eight studies with 2720 participants. The authors concluded that:

- The evidence suggests that rituximab (two 1,000 mg doses) in combination with methotrexate (MTX) is significantly more efficacious than MTX alone for improving the symptoms of RA and preventing disease progression.
- Rituximab improved pain, physical function, quality of life, and other symptoms of RA.
- Rituximab reduced disease activity and joint damage (as seen on x-ray).
- The rate of serious adverse events was comparable between patients receiving rituximab and MTX versus patients receiving MTX alone.

### ***Multiple Sclerosis***

A 2013 Cochrane review was published evaluating rituximab for relapsing-remitting multiple sclerosis (RRMS).<sup>100</sup> Authors concluded that:

- The beneficial effects of rituximab for RRMS remain inconclusive because of the high attrition bias, the small number of participants and the short follow-up in the available studies.
- The beneficial effects of rituximab remain inconclusive; however short-term treatment with a single course of rituximab was safe for most patients with RRMS.
- The potential benefits of rituximab for treating RRMS need to be evaluated in large scale studies that are of high quality along with long-term safety.

## **Professional Societies**

### ***Immune Thrombocytopenia***

The American Society of Hematology has published a comprehensive guideline on immune thrombocytopenia (ITP). The use of rituximab is suggested in the following clinical scenarios:<sup>74</sup>

- In adults with newly diagnosed ITP and a platelet count of  $< 30 \times 10^9/L$  who are asymptomatic or have minor mucocutaneous bleeding, the American Society of Hematology (ASH) guideline panel recommends treatment with corticosteroids. Second line therapies for treatment of ITP include Rituximab, TPO-RA, and splenectomy.
- The ASH guidelines recommend that each of these second-line treatments may be effective therapy and therefore the choice of treatment should be individualized based on duration of ITP, frequency of bleeding episodes requiring hospitalization or rescue medication, comorbidities, age of the patient, medication adherence, medical and social support networks, patient values and preferences, cost, and availability.
- Rituximab may be considered for children or adolescents with ITP who have significant ongoing bleeding despite treatment with IVIg, anti-D, or conventional doses of corticosteroids. Other second line therapies include TPO-RA and splenectomy.

### ***Neuromyelitis Optica***

The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology has published an evidence-based guideline on the clinical evaluation and treatment of transverse myelitis (TM).<sup>95</sup> The guideline included

statements regarding Neuromyelitis Optica (NMO), one of the main etiologies of transverse myelitis. Based on their review of two available Class III studies, the subcommittee issued a Level C recommendation for rituximab in the treatment of NMO. Rituximab may be considered in patients with TM due to NMO to decrease the number of relapses.

## U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

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.<sup>1</sup>

Rituxan is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20 - positive CLL.<sup>1</sup>

Rituxan in combination with methotrexate is indicated for the treatment of adult patients with moderately- to severely-active rheumatoid arthritis (RA) who have had an inadequate response to one or more TNF antagonist therapies.<sup>1</sup>

Rituxan in combination with glucocorticoids, is indicated for the treatment of adult and pediatric patients 2 years of age and older with Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) (WG) and Microscopic Polyangiitis (MPA).<sup>1</sup>

Rituxan is indicated for moderate to severe Pemphigus Vulgaris in adult patients.<sup>1</sup>

The FDA issued an alert dated September 25, 2013, to highlight additional Boxed Warning information about Rituxan. In patients with prior Hepatitis B virus (HBV) infection, HBV reactivation may occur when the body's immune system is impaired. HBV reactivation cases continue to occur, including deaths, prompting the alert. The FDA recommends thorough patient screening and monitoring of patients with prior HBV infection before and throughout therapy with Rituxan.<sup>103</sup>

Ruxience and Riabni are indicated for adult patients with:

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell Non-Hodgkin's Lymphoma (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 a rituximab product 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 cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.
- Previously untreated diffuse large B - cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens.
- In combination with fludarabine and cyclophosphamide (FC), for the treatment of adult patients with previously untreated and previously treated CD20-positive CLL.
- In combination with glucocorticoids, is indicated for the treatment of adult patients with Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA).<sup>68,116</sup>

Truxima is indicated for the treatment of adult patients with:

- Relapsed or refractory, low grade or follicular, CD20 - positive B-cell Non-Hodgkin's Lymphoma (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 a rituximab product 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 cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.

- Previously untreated diffuse large B - cell, CD20-positive NHL in combination with CHOP or other anthracycline - based chemotherapy regimens.
- RA in combination with methotrexate in adult patients with moderately - to severely - active RA who have inadequate response to one or more TNF antagonist therapies.
- GPA and MPA in adult patients in combination with glucocorticoids.<sup>109</sup>

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## Policy History/Revision Information

Date	Summary of Changes
11/01/2025	<p><b>Coverage Rationale</b></p> <p><b>Rheumatoid Arthritis</b></p> <ul style="list-style-type: none"> <li>• Updated list of examples of targeted immunomodulators the patient must not be receiving in combination with rituximab; added:               <ul style="list-style-type: none"> <li>○ Olumiant (baricitinib)</li> <li>○ Orencia (abatacept)</li> <li>○ Rinvoq (upadacitinib)</li> </ul> </li> </ul> <p><b>Neuromyelitis Optica</b></p> <ul style="list-style-type: none"> <li>• Updated list of examples of drug products the patient must not be receiving in combination with rituximab; added:               <ul style="list-style-type: none"> <li>○ Kevzara (sarilumab)</li> <li>○ Ultomiris (ravulizumab)</li> </ul> </li> </ul> <p><b>Immunoglobulin G4-Related Disease (IgG4-RD)</b></p> <ul style="list-style-type: none"> <li>• Added language to indicate rituximab is medically necessary for the treatment of IgG4-RD; rituximab is medically necessary for the treatment of IgG4-RD when all of the following criteria are met:</li> </ul> <p><b>Initial Therapy</b></p> <ul style="list-style-type: none"> <li>○ Diagnosis of IgG4-RD</li> <li>○ Confirmation of IgG4-RD by a positive assessment using the ACR/EULAR classification criteria, demonstrated by all of the following:               <ul style="list-style-type: none"> <li>▪ Involvement of at least 1 or more organ(s) in a manner consistent with IgG4-RD</li> <li>▪ Exclusion criteria is negative and consistent with an IgG4-RD diagnosis (e.g., clinical findings, serologic results, radiology assessments, pathology interpretations)</li> <li>▪ Inclusion criteria is positive and signifies a diagnosis of IgG4-RD (e.g., clinical findings, serologic results, radiology assessments, pathology interpretations)</li> </ul> </li> <li>○ Prescribed by, or in consultation with, a specialist with expertise in the treatment of IgG4-RD</li> <li>○ Patient is not receiving rituximab in combination with a disease modifying therapy for the treatment of IgG4-related disease [e.g., Uplizna (inebilizumab-cdon)]</li> <li>○ Initial authorization will be for no more than 12 months</li> </ul> <p><b>Continuation of Therapy</b></p> <ul style="list-style-type: none"> <li>○ Documentation of positive clinical response</li> </ul>

Date	Summary of Changes
	<ul style="list-style-type: none"> <li>○ Prescribed by, or in consultation with, a specialist with expertise in the treatment of IgG4-RD</li> <li>○ Patient is not receiving rituximab in combination with a disease modifying therapy for the treatment of IgG4-related disease [e.g., Uplizna (inebilizumab-cdon)]</li> <li>○ Reauthorization will be for no more than 12 months</li> </ul> <p><b>Applicable Codes</b></p> <ul style="list-style-type: none"> <li>● Added ICD-10 diagnosis code D89.84</li> </ul> <p><b>Supporting Information</b></p> <ul style="list-style-type: none"> <li>● Updated <i>Clinical Evidence</i> and <i>References</i> sections to reflect the most current information</li> <li>● Archived previous policy version CSPA2025D0003AN</li> </ul>

## Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.