

RITUXIMAB (RITUXAN® & TRUXIMA®)

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[Instructions for Use](#) ⓘ

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Related Commercial Policies

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COVERAGE RATIONALE

 See [Benefit Considerations](#) ⓘ

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

- Rituxan® (rituximab)
- Truxima® (rituximab-abbs)

“Rituximab” will be used to refer to both Rituxan and Truxima.

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

Rituximab is proven for the treatment of:

I. Immune thrombocytopenic purpura (ITP)^{2,4-16,74,75}

Additional information to support medical necessity review where applicable:

Rituximab is medically necessary for the treatment of immune thrombocytopenic purpura when all of the following criteria are met:

- A. Diagnosis of immune thrombocytopenic purpura (ITP); **and**
- B. Documented platelet count < 50 x 10⁹ / L; **and**
- C. History of failure, contraindication, or intolerance to **one** of the following:
 1. Anti-D immunoglobulin
 2. Corticosteroids
 3. Immune globulin
 4. Splenectomy

II. Autoimmune mucocutaneous blistering diseases (e.g. pemphigus vulgaris)^{1,3,17-26}

III. Wegener’s granulomatosis or microscopic polyangiitis (both ANCA-associated vasculidities)^{1,28-32,75}

Additional information to support medical necessity review where applicable:

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

- A. Diagnosis of Wegener’s granulomatosis or microscopic polyangiitis; **and**
- B. **One** of the following:
 1. Patient is receiving concurrent therapy with glucocorticoids
 2. History of contraindication or intolerance to glucocorticoids

IV. **Autoimmune hemolytic anemia, including chronic cold agglutinin disease**^{9,33-50,101-2,}

V. **Rheumatoid arthritis**^{1,75,77}

Additional information to support medical necessity review where applicable:

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

- A. Moderate to severe disease activity [e.g., swollen, tender joints with limited range of motion]; **and**
- B. **One** of the following:
 1. Patient is receiving concurrent therapy with methotrexate
 2. History of contraindication or intolerance to methotrexate**and**
- C. History of failure, contraindication or intolerance to at least **one** tumor necrosis factor (TNF) inhibitors [e.g., adalimumab (Humira), etanercept (Enbrel), infliximab (Remicade)]; **and**
- D. Patient is not receiving rituximab in combination with either of the following:
 1. Biologic DMARD [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
 2. Janus kinase inhibitor [e.g., Xeljanz (tofacitinib)]

VI. **Post-transplant B-lymphoproliferative disorder**⁷⁸

VII. **Neuromyelitis optica**^{32,53,77,79,94-95}

VIII. **Immunotherapy-related encephalitis**¹⁰⁸

Additional information to support medical necessity review where applicable:

Rituximab is medically necessary for the treatment of immunotherapy-related encephalitis when all of the following criteria are met:

- A. Diagnosis of immunotherapy-related encephalitis; **and**
- B. Recent immunotherapy treatment with a checkpoint inhibitor [e.g., Keytruda (pembrolizumab), Opdivo (nivolumab), Tecentriq (atezolizumab)]; **and**
- C. **One** of the following:
 1. Patient has had limited or no improvement after treatment with glucocorticoids for a minimum of 7 days; **or**
 2. History of contraindication or intolerance to glucocorticoids; **or**
 3. **Both** of the following:
 - a. Patient is positive for autoimmune encephalopathy antibody; **and**
 - b. Infectious causes (e.g., viral) of encephalitis have been ruled out

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

- Anti-GM1 antibody-related neuropathies
- Kaposi sarcoma-associated herpes virus-related multicentric Castleman disease
- Pure red cell aplasia
- Systemic lupus erythematosus
- Acquired factor VIII inhibitors
- Polyneuropathy associated with anti-MAG antibodies
- Idiopathic membranous nephropathy
- Chronic graft-versus-host disease
- Reduction of anti-HLA antibodies in patients awaiting renal transplant
- Multiple sclerosis
- Dermatomyositis and polymyositis

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.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

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.¹

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

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.¹

Rituxan in combination with glucocorticoids, is indicated for the treatment of adult patients with Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) (WG) and Microscopic Polyangiitis (MPA).¹

Rituxan is indicated for moderate to severe Pemphigus Vulgaris in adult patients.¹

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.¹⁰³

Truxima is indicated for the treatment of adult patients with:

- Non-Hodgkin’s Lymphoma
- 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 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.¹⁰⁹

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*.¹

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 the member specific benefit plan document 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 Coverage Determination Guidelines may apply.

HCPCS Code	Description
J9312	Injection, rituximab, 10 mg

ICD-10 Diagnosis Code	Description
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)
D59.0	Drug-induced autoimmune hemolytic anemia
D59.1	Other autoimmune hemolytic anemias
D69.3	Immune thrombocytopenic purpura
G04.81	Other encephalitis and encephalomyelitis
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

ICD-10 Diagnosis Code	Description
L10.3	Brazilian pemphigus [fogo selvagem]
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
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

ICD-10 Diagnosis Code	Description
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
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

ICD-10 Diagnosis Code	Description
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
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

ICD-10 Diagnosis Code	Description
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
M05.70	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
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

ICD-10 Diagnosis Code	Description
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
M05.80	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
M06.00	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
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

ICD-10 Diagnosis Code	Description
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
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

ICD-10 Diagnosis Code	Description
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
M06.80	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
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
M31.30	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

ICD-10 Diagnosis Code	Description
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

BENEFIT CONSIDERATIONS

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

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.² 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/m² 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 were 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.³ 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.²⁸ Study subjects had either warm (W) AIHA (n=18) or cold hemagglutinin disease (CHD) (n=14) and received LD rituximab (100 mg fixed dose \times 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 μ g/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).²⁹ 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.⁴⁸ 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/m² 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 nonresponders 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 nonresponders and improvements in clinical symptoms occurred in 6 of 17 nonresponders. 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.⁴⁹ 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/m² 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.⁷⁸

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.⁷⁸

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.⁷⁸

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/m² infusions.³² 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.⁵³ After induction therapy, a single infusion of rituximab (375 mg/m²) 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.⁷⁷ 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.⁷⁹ 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).⁹⁴ Thirty patients with relapsing NMO or NMO spectrum disorder received a treatment protocol of rituximab induction therapy (375 mg/m² once weekly for 4 weeks or 1000 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/m², 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.

Unproven

Systemic Lupus Erythematosus

Rovin et al. conducted the LUNAR study to investigate whether the addition of rituximab to a background of mycophenolate mofetil (MMF) plus corticosteroids in patients with proliferative lupus nephritis (LN) could improve renal response rates at 52 weeks.⁵¹ Their randomized, double-blind, placebo-controlled phase III trial enrolled 144 patients with Class III or IV lupus nephritis. Subjects were randomized 1:1 to rituximab (1000 mg) or placebo on days 1, 15, 168, and 182. The primary efficacy endpoint was renal response, defined as complete renal response (CRR), partial renal response (PRR), or no response (NR), at Week 52. Criteria for a CRR included: normal serum creatinine (SCr) if abnormal at baseline, or SCr \leq 115% of baseline if normal at baseline; inactive urinary sediment ($<$ 5 RBC/HPF and absence of RBC casts); and UPC $<$ 0.5. Patients who achieved PRR were defined as not meeting CRR, but having SCr \leq 115% of baseline; RBC/HPF \leq 50% above baseline and no RBC casts; and at least a 50% decrease in UPC to $<$ 1.0 (if baseline UPC was \leq 3.0), or to \leq 3.0 (if baseline UPC was $>$ 3.0). Patients were monitored every 4 weeks. Monitoring extended through week 78 in order to assess the long-lasting pharmacodynamic effects of rituximab and the relapsing nature of LN in the months post-treatment. Overall renal response rates (CRR or PRR) were 56.9% for rituximab and 45.8% for placebo ($p=0.18$), with the difference attributable to higher PRR rates. The primary endpoint

(superior response rate with rituximab) was not achieved. Rates of serious adverse events, including infections, were similar in both groups. The investigators concluded that rituximab did not improve clinical outcomes after 1 year of treatment.

In the EXPLORER trial, Merrill et al. assessed the response to rituximab versus placebo in patients with moderate to severe extrarenal systemic lupus erythematosus (SLE) receiving background immunosuppression.⁵² Eligible patients (n=257) had a British Isles Lupus Assessment Group (BILAG) A score ≥ 1 or a BILAG B score ≥ 2 despite immunosuppressive therapy. Patients were randomized to a 2:1 ratio to receive intravenous rituximab (two 1,000-mg doses given 14 days apart, n=169) or placebo (n=88) on days 1, 15, 168, and 182, which was added to prednisone (given according to the protocol) and to the baseline immunosuppressive regimen. Primary endpoints measured were the effect of placebo versus rituximab in achieving and maintaining a major clinical response, a partial clinical response, or no clinical response. The definition of response required reduced clinical activity without subsequent flares over 52 weeks. Subjects were assessed monthly with the BILAG index and the Lupus Quality of Life Index. At week 52, no difference was noted in major clinical responses or partial clinical responses between the placebo group (15.9% had a major clinical response, and 12.5% had a partial clinical response) and the rituximab group (12.4% had a major clinical response, and 17.2% had a partial clinical response) relative to the overall response rate (28.4% versus 29.6%). In summary, the EXPLORER trial demonstrated no difference in primary or secondary endpoints between the placebo group and the rituximab group over 52 weeks of treatment, in patients with moderate-to-severe SLE.

A small open label, multi-centered study of 15 patients with active refractory systemic lupus erythematosus (SLE) was conducted.⁵² Patients were assessed for disease severity at weeks 2, 4, 8, 12, 16, 20, 24, and 28 based on the British Isles Lupus Assessment Group (BILAG). Clinical responses were grouped at 28 weeks into: major clinical response (MCR) defined as achieving BILAG C or better; partial clinical response (PCR) defined as achieving max of one domain with BILAG B; and no clinical response (NCR) if patient didn't meet either of the above. Statistical significance was seen at weeks 4, 16, and 28 in BILAG scores as compared to baseline ($p < 0.001$) in 14 patients. Two patients met MCR, 7 met PCR, and 5 NCR. The study concluded that rituximab appears safe for active refractory SLE and holds significant therapeutic promise.

An open label longitudinal analysis was conducted on 24 patients with severe systemic lupus erythematosus (SLE) who were followed for a minimum of 3 months.⁵³ In the majority of patients (19 out of 24), 6 months follow-up data were described. Disease activity in these patients was assessed every 1-2 months using the British Isles Lupus Assessment Group (BILAG) system and estimates of anti-double-stranded DNA antibodies and serum C3 levels. During the follow-up period, significant side effects and reduction in oral prednisolone were recorded. The general practice was to stop concomitant immunosuppression (e.g., azathioprine, mycophenolate) when B-cell depletion was given (in most cases in the form of two 1 g intravenous infusions of rituximab 2 weeks apart accompanied by two 750 mg intravenous cyclophosphamide infusions and two methylprednisolone infusions of 250 mg each). The results included 22 female patients, and two males. At the time of B-cell depletion, the mean age was 28.9 yr (range 17-49) and the mean disease duration was 7.9 yr (range 1-18). The global BILAG score ($p < 0.00001$), serum C3 ($p < 0.0005$) and double-stranded DNA binding ($p < 0.002$) all improved from the time of B-cell depletion to 6 months after this treatment. Only one patient failed to achieve B-lymphocyte depletion in the peripheral blood. The period of B-lymphocyte depletion ranged from 3 to 8 months except for one patient who remains depleted at more than 4 yr. Analysis of the regular BILAG assessments showed that improvements occurred in each of the eight organs or systems. The mean daily prednisolone dose fell from 13.8 mg (s.d 11.3) to 10 mg (s.d 3.1). In conclusion, this open label study of patients who had failed conventional immunosuppressive therapy showed considerable utility in the use of B-cell depletion.

Additional small, open-label trials of rituximab with^{54,58-61} or without⁶²⁻⁶⁷ cyclophosphamide have been conducted in SLE patients with results similar to those of the above trials.

Multiple Sclerosis

Rituximab was evaluated as add-on therapy for breakthrough relapsing remitting multiple sclerosis (RRMS) in a 52-week, phase II trial involving 30 patients.⁶⁸ Study participants received rituximab 375 mg/m² weekly for four doses. Patients were assessed using post-treatment brain MRI scans monthly x 3 scans, beginning 12 weeks after the first infusion. In addition, subjects were measured according to the Multiple Sclerosis Functional Composite (MSFC) and Expanded Disability Status Scale (EDSS) at baseline and throughout the post-treatment follow-up period. The investigators observed a reduction of gadolinium-enhancing (GdE) lesions after treatment with rituximab, with 74% of scans being free of GdE lesions post-treatment compared to 26% free at baseline ($p < 0.0001$). After treatment, median GdE lesions were reduced from 1.0 to 0, and mean number of lesions was reduced by 88% (from 2.81 to 0.33 per month). MSFC was observed to improve after treatment, while EDSS remained stable. By targeting B-cells, rituximab provides a potential option for treatment of patients with relapsing MS with an inadequate response to standard injectable therapies. However, this is an uncontrolled study including small numbers of participants, so the significance of these conclusions is uncertain.

A phase II, double-blind trial of 104 relapsing-remitting multiple sclerosis patients given rituximab 1000mg IV (n=69) or placebo (n=35) on days 1 and 15 assessed the primary end point of total count of gadolinium-enhancing lesions detected on magnetic resonance imaging scans of the brain at weeks 12,16, 20, and 24.⁶⁹ Clinical outcomes also included safety, proportion of patients with relapses, and annualized rate of relapse. Reduction in total gadolinium-enhancing lesions was statistically reduced at all weeks (p<0.001), as was reduction in total new gadolinium-enhancing lesions over the same period (p<0.001). The results were sustained for 48 weeks. The proportion of rituximab patients with relapses compared to placebo 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). Adverse events (mostly mild-to-moderate) were more common in the rituximab group within 24 hours of the first infusion, but not with the second infusion. However, the investigators note that the trial was not designed to assess long-term safety or to detect uncommon adverse events.

Miscellaneous

Rituximab has been used in the treatment of other conditions. These include anti-GM1 antibody-related neuropathies,⁷²⁻⁷³ Kaposi sarcoma-associated herpes virus-related multicentric Castleman disease,^{80,105} pure red cell aplasia,⁸¹⁻⁸² acquired factor VIII inhibitors,⁸³⁻⁸⁴ polyneuropathy associated with anti-MAG antibodies,^{85,101-2,104} idiopathic membranous nephropathy,⁸⁶⁻⁸⁸ chronic graft-versus-host disease^{27,50,51,76,89-92,106} reduction of anti-HLA antibodies in patients awaiting renal transplant,⁹³ and dermatomyositis and polymyositis.⁹⁶⁻⁹⁹ 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.¹⁰⁷ The review evaluated eight studies with 2720 participants. The authors concluded that:

- The evidence suggests that rituximab (two 1000 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).¹⁰⁰ 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:⁷⁴

- Rituximab be considered for children or adolescents with ITP who have significant ongoing bleeding despite treatment with IVIg, anti-D, or conventional doses of corticosteroids.
- Rituximab may also be considered as an alternative to splenectomy in children and adolescents with chronic ITP or in patients who do not respond favorably to splenectomy.
- Rituximab may be considered for patients at risk of bleeding who have failed one line of therapy such as corticosteroids, IVIg, or 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).⁹⁵ 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.

Medicare does not have a National Coverage Determination (NCD) for rituximab (Rituxan®). Local Coverage Determinations (LCDs) exist; see the LCDs for [Rituximab \(Rituxan®\)](#).

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the [Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals](#). (Accessed January 11, 2019)

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
04/01/2019	Annual review of policy. Added Truxima. Updated coverage rationale, CMS statement and references. Policy 2019D0003T archived.
03/01/2019	Reorganized policy template; simplified and relocated <i>Instructions for Use and Benefit Considerations</i> section. Policy 2019D0003S archived.
01/01/2019	Updated list of applicable HCPCS codes to reflect annual code edits; replaced J9310 with J9312. Policy 2018D0003R archived.

Date	Action/Description
04/01/2018	Annual review of policy. Updated coverage rational, CMS statement and references. Approved by the National Pharmacy & Therapeutics Committee on 03/21/2018. Policy 2016D0003Q archived.
07/01/2017	Annual review of policy. Transferred to new template. Updated criteria for ITP. Updated clinical evidence, CMS statement, and references. Removed ICD-9 codes. Approved by the National Pharmacy & Therapeutics Committee on 04/26/2017. Policy 2016D0003P archived.
07/01/2016	Annual review of policy with no changes to coverage rationale. Updated CMS statement and references. Approved by the National Pharmacy & Therapeutics Committee on 05/20/2016. Policy 2015D0003O archived.
10/01/2015	Updated Applicable Codes for ICD-10 transition. Policy 2015D0003N archived.
07/01/2015	Annual review of policy. Updated benefit considerations with ACA language. Consolidated clinical evidence for proven and unproven uses. Added ICD-9 code 714.89. Updated references. Approved by the National Pharmacy & Therapeutics Committee 04/14/2015. Policy 2014D0003M archived.
06/01/2014	Annual review of policy. Revised criteria for ITP, Wegener's granulomatosis, microscopic polyangiitis, and rheumatoid arthritis. Updated clinical evidence and references. Approved by the National Pharmacy & Therapeutics Committee 04/08/2014. Policy 2013D0003L archived.
06/01/2013	Annual review of policy. Changed idiopathic thrombocytopenic purpura (ITP) to immune thrombocytopenic purpura. Added medical necessity criteria for ITP, Wegener's granulomatosis, microscopic polyangiitis, and rheumatoid arthritis. Post-transplant lymphoproliferative disorder and neuromyelitis optica changed to proven diagnoses. Updated clinical evidence and references. Updated list of ICD-9 codes (added 238.77 and 341.0) and associated ICD-10 codes. Approved by the National Pharmacy & Therapeutics Committee 04/09/2013. Policy 2012D0003K archived.
09/01/2012	Added list of applicable ICD-10 codes (preview draft) in preparation for the transition from ICD-9 to ICD-10 medical coding on 10/01/2014.
06/01/2012	Annual review of policy. Clinical evidence and references updated. Approved by the National Pharmacy & Therapeutics Committee 04/10/2012. Policy 2011D0003J archived.
09/01/2011	Policy revised. Added microscopic polyangiitis to proven uses. Added ICD-9 code 446.0. Added neuromyelitis optica, dermatomyositis, and polymyositis to unproven uses. Added Hayes Technology Brief on SLE. References updated. Approved by National Pharmacy & Therapeutics Committee 07/12/2011. Email ballot to clarify language in Coverage Rationale approved on 08/29/2011. Policy 2010D0003I archived.
12/01/2010	Policy revised. Autoimmune hemolytic anemia, including chronic cold agglutinin disease, changed to proven diagnosis. Added Additional Information section within Coverage Rationale. Added FDA Section which includes approved indications and FDA Alert. Approved by National Pharmacy & Therapeutics Committee 11/09/2010. Policy 2009D0003H archived.
10/30/2009	Policy revised. Waldenstrom's macroglobulinemia and additional references to oncology indications removed from policy. Autoimmune mucocutaneous blistering diseases changed to proven diagnosis. Juvenile rheumatoid arthritis ICD-9 codes deleted from approved diagnosis list. Approved by National Pharmacy & Therapeutics Committee on 08/11/2009. Policy 2008D0003G archived.
12/18/2008	ICD9 coding for ITP, Wegeners, and Macroglobulinemia added.
04/16/2008	Policy revised with changes in coverage rationale. Approved by National Pharmacy & Therapeutics Committee on 04/08/2008. Policy 2006D003F archived.

INSTRUCTIONS FOR USE

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal

or state mandates. 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.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence ([Medicare IOM Pub. No. 100-16, Ch. 4, §90.5](#)).

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. 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.