

Rituximab (Riabni™, Rituxan®, Ruxience®, & Truxima®)

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[Instructions for Use](#)

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Related Community Plan Policies
<ul style="list-style-type: none"> Maximum Dosage and Frequency Off-Label/Unproven Specialty Drug Treatment Oncology Medication Clinical Coverage
Commercial Policy
<ul style="list-style-type: none"> Rituximab (Riabni™, Rituxan®, Ruxience®, & Truxima®)

Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Indiana	Rituximab (Riabni™, Rituxan®, Ruxience®, & Truxima®) (for Indiana Only)
Kansas	None
Louisiana	Rituximab (Riabni™, Rituxan®, Ruxience®, & Truxima®) (for Louisiana Only)
North Carolina	None
Ohio	Rituximab (Riabni™, Rituxan®, Ruxience®, & Truxima®) (for Ohio Only)

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 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:
 - 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
 - One of the following:
 - History of intolerance, contraindication, or adverse event to Truxima; or
 - History of intolerance, contraindication, or adverse event to Ruxienceand
- 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
 - 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
 - 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)^{2,4-16,74,75}

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 10⁹ / 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])
 - Splenectomyand
- Initial authorization will be for no more than 3 months.

For continuation of therapy:

- Reauthorization will be for no more than 3 months.

- Pemphigus vulgaris^{1,3,17-26}

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
- Used in combination with a tapering course of glucocorticoids; and
- Initial authorization will be for no more than 6 months.

For continuation of therapy:

- Reauthorization will be for no more than 12 months.

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

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 3 months.

For continuation of therapy:

- Reauthorization will be for no more than 12 months.

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

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 3 months.

For continuation of therapy:

- Reauthorization will be for no more than 3 months.

- Rheumatoid arthritis^{1,75,77}

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 either of the following:
 - Biologic DMARD [e.g., Enbrel (etanercept), adalimumab, Cimzia (certolizumab), Simponi (golimumab)]
 - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib)];and
- Initial authorization will be for no more than 6 months.

For continuation of therapy:

- Reauthorization will be for no more than 12 months.

- Post-transplant B-lymphoproliferative disorder (PTLD)⁷⁸

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 6 months.

For continuation of therapy:

- Reauthorization will be for no more than 12 months.

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

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):²⁵
 - 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; and
 - 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)]
 - Complement inhibitors [e.g., Soliris (eculizumab)];and
- Initial authorization will be for no more than 6 months.

For continuation of therapy, all 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)]
 - Complement inhibitors [e.g., Soliris (eculizumab)];and
- Reauthorization will be for no more than 12 months.

- Immunotherapy-related encephalitis¹⁰⁸

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
- Initial authorization will be for no more than 3 months.

For continuation of therapy:

- Reauthorization will be for no more than 3 months.

- Thrombotic thrombocytopenic purpura (TTP)¹¹⁰⁻¹¹²

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
- Initial authorization will be for no more than 3 months.

For continuation of therapy:

- Reauthorization will be for no more than 3 months.

- Multiple sclerosis (MS)^{69,70,113-116}

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
- o Initial authorization will be for no more than 6 months.

For continuation of therapy, all of the following:

- o 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
- o 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
- 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
- Reduction of anti - HLA antibodies in patients awaiting renal transplant
- 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.

*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 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-pwv, biosimilar, (ruxience), 10 mg
Q5123	Injection, rituximab-arx, 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

Diagnosis Code	Description
D59.13	Mixed type autoimmune hemolytic anemia
D59.19	Other autoimmune hemolytic anemia
D69.3	Immune thrombocytopenic purpura
G04.81	Other encephalitis and encephalomyelitis
G35	Multiple sclerosis
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

Diagnosis Code	Description
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
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

Diagnosis Code	Description
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
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

Diagnosis Code	Description
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
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

Diagnosis Code	Description
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
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

Diagnosis Code	Description
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
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

Diagnosis Code	Description
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
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

Diagnosis Code	Description
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
M31.10	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.¹

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 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.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 upon 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 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/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.

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.¹¹¹ 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 thrombotic 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.¹¹² 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 × 10⁹/L and 38% > 150 × 10⁹/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 15.⁶⁹ 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])

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 (1,000 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 ≤ 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 ≤ 115% of baseline; RBC/HPF ≤ 50% above baseline and no RBC casts; and at least a 50% decrease in UPC to < 1.0 (if baseline UPC was ≤ 3.0), or to ≤ 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 at 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 end points 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.

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 Castlemans 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 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).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

- 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).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.

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.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 (RA) 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 and pediatric patients 2 years of age and older 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

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)^{68,116}

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 glucocorticoids¹⁰⁹

References

1. Rituxan [prescribing information]. South San Francisco, CA: Genentech, Inc.; August 2020.
2. Gudbrandsdottir S, Birgens HS, Frederiksen H, et al. Rituximab and dexamethasone vs dexamethasone monotherapy in newly diagnosed patients with primary immune thrombocytopenia. *Blood*. 2013 Mar 14;121(11):1976-81. doi: 10.1182/blood-2012-09-455691. Epub 2013 Jan 4.
3. Heelan K, Al-Mohammed F, Smith MJ, et al. Durable Remission of Pemphigus With a Fixed-Dose Rituximab Protocol. *JAMA Dermatol*. 2014 Feb 5. doi: 10.1001/jamadermatol.2013.6739. [Epub ahead of print].
4. Cooper N, Stasi R, Cunningham-Rundles S, et al. The efficacy and safety of B-cell depletion with anti-CD20 monoclonal antibody in adults with chronic immune thrombocytopenic purpura. *Br J Haematol* 2004;125:232-239.
5. Godeau B, Porcher R, Fain O, et al. Rituximab efficacy and safety in adult splenectomy candidates with chronic immune thrombocytopenic purpura: results of a prospective multicenter phase 2 study. *Blood*. 2008;112(4):999-1004.
6. Stasi R, Pagano A, Stipa E, Amadori S. Rituximab chimeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura. *Blood* 2001;98:952-957.
7. Saleh MN, Gutheil J, Moore M, et al. A pilot study of the anti-CD20 monoclonal antibody rituximab in patients with refractory immune thrombocytopenia. *Semin Oncol* 2000;27(suppl 12):99-103.
8. Delgado J, Bustos JG, Jimenez-Yuste V, Hernandez-Navarro F. Anti-CD20 monoclonal antibody therapy in refractory immune thrombocytopenic purpura. *Haematologica* 2002;87:215-216.

9. Zaja F, Iacona I, Masolini P, et al. B-cell depletion with rituximab as treatment for immune hemolytic anemia and chronic thrombocytopenia. *Haematologica* 2002;87:189-195.
10. Giagounidis AAN, Anhu J, Schneider P, et al. Treatment of relapsed idiopathic thrombocytopenic purpura with the anti-CD20 monoclonal antibody rituximab: a pilot study. *Eur J Haematol* 2002;69:95-100.
11. Garcia-Chavez J, Majluf-Cruz, Montiel-Cervantes L, et al. Rituximab therapy for chronic and refractory immune thrombocytopenic purpura: a long-term follow-up analysis. *Ann Hematol.* 2007;86(12):871-7.
12. Mueller BU, Bennett CM, Feldman HA, et al. One year follow-up of children and adolescents with chronic immune thrombocytopenic purpura (ITP) treated with rituximab. *Pediatr Blood Cancer.* 2009 Feb;52(2):259-62.
13. Wang W, Yu Qh, Zhang HY et al. [Rituximab treatment for adults with steroid-resistant idiopathic thrombocytopenic purpura]. *Zhonghua Nei Ke Za Zhi.* 2008 Mar;47(3):225-7.
14. Provan D, Butler T, Evangelista ML, et al. Activity and safety profile of low-dose rituximab for the treatment of autoimmune cytopenia in adults. *Haematologica.* 2007 Dec;92(12):1695-8.
15. Narang M, Penner JA, Williams D. Refractory autoimmune thrombocytopenic purpura: responses to treatment with a recombinant antibody to lymphocyte membrane antigen CD20 (rituximab). *Am J Hematol.* 2003 Dec;74(4):263-7.
16. Meo P, Stipa E, La Presa M, et al. [Rituximab treatment of chronic idiopathic thrombocytopenic purpura. Results of a phase II study]. *Recenti Prog Med.* 2002 Jul-Aug;93(7-8):421-7.
17. Joly P, Mouquet H, Roujea JC. A Single cycle of Rituximab for the Treatment of Severe Pemphigus. *N Eng J Med.* 2007. 357(6):545-52.
18. Ahmed AR, Spigelman Z, Cavacini LA. Treatment of Pemphigus Vulgaris with Rituximab and Intravenous Immune Globulin. *N Eng J Med.* 2006. 355(17):1772-9.
19. Salopek TG, Logsetty S, Tredget EE. Anti-CD20 chimeric monoclonal antibody (rituximab) for the treatment of recalcitrant, life-threatening pemphigus vulgaris with implications in the pathogenesis of the disorder. *J Am Acad Dermatol* 2002;47:785-788.
20. Dupuy A, Viguier M, Bedane C, et al. Treatment of refractory pemphigus vulgaris with rituximab (anti-CD20 monoclonal antibody). *Arch Dermatol* 2004;140:91-96.
21. Faurichou A, Gniadecki R. Two courses of rituximab (anti-CD20 monoclonal antibody) for recalcitrant pemphigus vulgaris. *Int J Dermatol.* 2008 Mar;47(3):292-4.
22. Barrera MV, Mendiola MV, Bosch RJ, Herrera E. Prolonged treatment with rituximab in patients with refractory pemphigus vulgaris. *J Dermatolog Treat.* 2007;18(5):312-4.
23. Esposito, M, Capriotti E, Giunta A, et al. Long-lasting remission of pemphigus vulgaris treated with rituximab. *Acta Dermato-Venereologica.* 2006. 86(1):87-9.
24. Wenzel J, Bauer R, Bieber T, Tuting T. Successful rituximab treatment of severe pemphigus vulgaris resistant to multiple immunosuppressants. *Acta Dermato-Venereologica.* 2005. 85(2):185-6.
25. Schmidt E, Herzog S, Brocker EB, et al. Long-standing remission of recalcitrant juvenile pemphigus vulgaris after adjuvant therapy with rituximab. *British Journal of Dermatology.* 2005. 153(2):449-51.
26. Hertl M, Zillikens D, Borradori L, et al. Recommendations for the use of rituximab (anti-CD20 antibody) in the treatment of autoimmune bullous skin diseases. *J Dtsch Dermatol Ges.* 2008 May;6(5):366-73. doi: 10.1111/j.1610-0387.2007.06602.x. Epub 2008 Jan 14.
27. Wolff D, Schleuning M, von Harsdorf S, Bacher U, Gerbitz A, Stadler M, Ayuk F, Kiani A, Schwerdtfeger R, Vogelsang GB, Kobbe G, Gramatzki M, Lawitschka A, Mohty M, Pavletic SZ, Greinix H, Holler E. Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease. *Biol Blood Marrow Transplant.* 2011 Jan;17(1):1-17.
28. Barcellini W, Zaja F, Zaninoni A, et al. Sustained response to low-dose rituximab in idiopathic autoimmune hemolytic anemia. *Eur J Haematol.* 2013 Dec;91(6):546-51. doi: 10.1111/ejh.12199. Epub 2013 Oct 3.
29. Birgens H, Frederiksen H, Hasselbalch HC, et al. A phase III randomized trial comparing glucocorticoid monotherapy versus glucocorticoid and rituximab in patients with autoimmune hemolytic anemia. *Br J Haematol.* 2013 Nov;163(3):393-9.

30. Maung SW, Leahy M, O'Leary HM, et al. A multi-centre retrospective study of rituximab use in the treatment of relapsed or resistant warm autoimmune hemolytic anemia. *Br J Haematol*. 2013 Oct;163(1):118-22.
31. Peñalver FJ, Alvarez-Larrán A, Díez-Martin JL, et al. Rituximab is an effective and safe therapeutic alternative in adults with refractory and severe autoimmune hemolytic anemia. *Ann Hematol*. 2010 Nov;89(11):1073-80.
32. Trebst C, Jarius S, Berthele A, et al. Update on the diagnosis and treatment of neuromyelitis optica: Recommendations of the Neuromyelitis Optica Study Group (NEMOS). *J Neurol*. 2014 Jan;261(1):1-16. doi: 10.1007/s00415-013-7169-7. Epub 2013 Nov 23.
33. D'Arena G, Califano C, Annunziata M, et al. Rituximab for warm-type idiopathic autoimmune hemolytic anemia: a retrospective study of 11 adult patients. *Eur J Haematol* 2007 July;79(1):53-8.
34. Quartier P, Brethon B, Philippet P, et al. Treatment of childhood autoimmune hemolytic anemia with rituximab. *Lancet* 2001;358:1511-1513.
35. Gupta N, Kavuru S, Patel D, et al. Rituximab-based chemotherapy for steroid-refractory autoimmune hemolytic anemia of chronic lymphocytic leukemia. *Leukemia* 2002;16:2092-2095.
36. Zecca M, Nobili B, Ramenghi U, et al. Rituximab for the treatment of refractory autoimmune hemolytic anemia in children. *Blood*. 2003;101(10):3857-61.
37. Rao A, Kelly M, Musselman M, et al. Safety, efficacy, and immune reconstitution after rituximab therapy in pediatric patients with chronic or refractory hematologic autoimmune cytopenia. *Pediatr Blood Cancer*. 2007;50(4):822-5.
38. Shanafelt TD, Madueme HL, Wolf RC, Tefferi A. Rituximab for immune cytopenia in adults: idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, and Evan syndrome. *Mayo Clin Proc*. 2003;78(11):1340-6.
39. Heidel F, Lipka DB, von Auer C, et al. Addition of rituximab to standard therapy improves response rate and progression-free survival in relapsed or refractory thrombotic thrombocytopenic purpura and autoimmune hemolytic anemia. *Throm Haemost* 2007 February;97(2):228-33.
40. Perrotta S, Locatelli F, La Manna A, et al. Anti-CD20 monoclonal antibody (rituximab) for life-threatening autoimmune hemolytic anemia in a patient with systemic lupus erythematosus. *Br J Haematol* 2002;116:465-467.
41. Svahn J, Fioredda F, Calvillo M, et al. Rituximab-based immunosuppression for auto immune hemolytic anemia in infants. *British Journal of Dermatology*. 2009;145(1):96-100.
42. Motto DG, Williams JA, & Boxer LA: Rituximab for refractory childhood autoimmune hemolytic anemia. *Isr Med Assoc J* 2002; 4(N11):1006-1008.
43. Narat S, Gandla J, & Mehta AB: Anti-CD20 monoclonal antibody in the treatment of refractory autoimmune cytopenia in adults. *Blood* 2004;104:742A.
44. Narat S, Gandla J, Hoffbrand AV, et al. Rituximab in the treatment of refractory autoimmune cytopenia in adults. *Haematologica*. 2005;90(9):1273-4.
45. Noel N, Monnet X, Angel N, Goujard C, Lambotte O. Life threatening steroid-resistant autoimmune anemia successfully treated with rituximab: a case report. *Am J Hematol*. 2009;84(3):193.
46. Garay G, Riveros D, Milone J, et al: Refractory autoimmune cytopenia, either associated with lymphoproliferative diseases or idiopathic in adult patients, treated with anti-CD20 monoclonal antibody (Rituximab). *Blood* 2004; 104(11, Part 2):238B.
47. D'Arena G, Laurenti L, Capalbo S, et al. Rituximab therapy for chronic lymphocytic leukemia-associated autoimmune hemolytic anemia. *Am J Hematol*. 2006;81(8):598-602.
48. Berentsen S, Ulvestad E, Gjertsen BT, et al. Rituximab for primary chronic cold agglutinin disease: a prospective study of 37 courses of therapy in 27 patients. *Blood* 2004;103:2925-2928.
49. Schöllkopf C, Kjeldsen L, Bjerrum OW, et al. Rituximab in chronic cold agglutinin disease: a prospective study of 20 patients. *Leuk Lymphoma*. 2006 Feb;47(2):253-260.
50. Kim SJ, Lee JW, Jung CW, Min CK, Cho B, Shin HJ, Chung JS, Kim H, Lee WS, Joo YD, Yang DH, Kook H, Kang HJ, Ahn HS, Yoon SS, Sohn SK, Min YH, Min WS, Park HS, Won JH. Weekly rituximab followed by monthly rituximab treatment for steroid-refractory chronic graft-versus-host disease: results from a prospective, multicenter, phase II study. *Haematologica*. 2010 Nov;95(11):1935-42.

51. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum*. 2012 Apr;64(4):1215-26.
52. Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum* 2010; 62(1):222-233.
53. Kim SH, Huh SY, Lee SJ, et al. A 5-year follow-up of rituximab treatment in patients with neuromyelitis optica spectrum disorder. *JAMA Neurol*. 2013 Sep 1;70(9):1110.
54. Tanaka Y, Kazuhiko Y, Takeuchi T, et al. A multi-center phase I/II trial of rituximab for refractory systemic lupus erythematosus. *Mod Rheumatol* 2007;17:191-197.
55. Leandro MJ, Cambridge G, et al. B-cell depletion in the treatment of patients with systemic lupus erythematosus: a longitudinal analysis of 24 patients. *Rheumatology (Oxford)*. 2005; 44(12):1542-5.
56. Marks SD, Patey S, Brogan PA, et al. B lymphocyte depletion therapy in children with refractory systemic lupus erythematosus. *Arthritis Rheum*. 2005;52(10):3168-74.
57. Anolik JH, Barnard J, et al. Rituximab improves peripheral B cell abnormalities in human systemic lupus erythematosus. *Arthritis Rheum*. 2004;50(11):3580-90.
58. Jonsdottier T, Gunnarsson I, Risselada A, et al. Treatment of refractory SLE with rituximab plus cyclophosphamide: clinical effects, serological changes, and predictors of response. *Ann Rheum Dis*. 2008 Mar;67(3):330-4.
59. Gunnarsson I, Sundalin B, Jonsdottier T, et al. Histopathologic and clinical outcome of rituximab treatment in patients with cyclophosphamide-resistant proliferative lupus nephritis. *Arthritis Rheum*. 2007;56(4):263-72.
60. Smith KG, Jones RB, Burns SM, et al. Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: Remission, relapse, and re-treatment. *Arthritis Rheum*. 2006;54(9):2970-82.
61. Willems M, Haddad E, Niaudet P, et al. Rituximab therapy for childhood-onset systemic lupus erythematosus. *J Pediatr*. 2006;148(5):623-7.
62. Looney RJ, Anolik JH, Campbell D, et al. B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab. *Arthritis Rheum*. 2004;50(8):2580-9.
63. Vigna-Perez M, Hernandez-Castro B, Paredes-Saharopoulos O, et al. Clinical and immunological effects of Rituximab in patients with lupus nephritis refractory to conventional therapy: a pilot study. *Arthritis Res Ther*. 2006;8(3):R83.
64. Cambridge G, Leandro MJ, Teodorescu M, et al. B cell depletion therapy in systemic lupus erythematosus: effect on autoantibody and antimicrobial antibody profiles. *Arthritis Rheum*. 2006 Nov;54(11):3612-22.
65. Cambridge G, Isenberg DA, Edwards JC, et al. B cell depletion therapy in systemic lupus erythematosus: relationships among serum B lymphocyte stimulator levels, autoantibody profile and clinical response. *Ann Rheum Dis*. 2008;67(7):1011-6.
66. Albert D, Dunham J, Khan S, et al. Variability in the biological response to anti-CD20 B cell depletion in systemic lupus erythematosus. *Ann Rheum Dis*. 2008;67(12):1724-31.
67. Tamimoto Y, Horiuchi T, Tsukamoto H, et al. A dose-escalation study of rituximab for treatment of systemic lupus erythematosus and Evans' syndrome: immunological analysis of B cells, T cells and cytokines. *Rheumatology (Oxford)*. 2008;47(6):821-7.
68. Ruxience [Prescribing information] New York, NY: Pfizer, Inc.; May 2020.
69. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Eng J Med*. 2008 Feb 14;358(7):676-88.
70. Bar-Or A, Calabresi PA, Arnold D, et al. Rituximab in relapsing-remitting multiple sclerosis: a 72-week, open-label, phase I trial. *Ann Neurol*. 2008 Mar;63(3):395-400.
71. Monson NL, Cravens PD, et al. Effect of rituximab on the peripheral blood and cerebrospinal fluid B cells in patients with primary progressive multiple sclerosis. *Arch. Neurol*. 2005;62(2):258-64.
72. Levine TD, Pestronk A. IgM antibody-related polyneuropathies: B-cell depletion chemotherapy using rituximab. *Neurology* 1999;52:1701-1704.

73. Kilidireas C, Anagnostopoulos A, Karandreas N, et al. Rituximab therapy in monoclonal IgM-related neuropathies. *Leuk Lymphoma*. 2006 May;47(5):859-64.
74. Neunert C, Terrell D, Arnold D, et al. The American Society of Hematology 2019 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2019 Dec 10;3(23):3829-3866.
75. MCG™ Care Guidelines, 22nd edition, 2018, Rituximab ACG:A-0448 (AC).
76. von Bonin M, Oelschlägel U, Radke J, Stewart M, Ehninger G, Bornhauser M, Platzbecker U. Treatment of chronic steroid-refractory graft-versus-host disease with low-dose rituximab. *Transplantation*. 2008 Sep 27;86(6):875-9.
77. Mealy MA, Wingerchuk DM, Palace J, et al. Comparison of Relapse and Treatment Failure Rates Among Patients With Neuromyelitis Optica: Multicenter Study of Treatment Efficacy. *JAMA Neurol*. 2014 Jan 20.
78. National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium® (NCCN Compendium®). Available at http://www.nccn.org/professionals/drug_compendium/MatrixGenerator/Matrix.aspx?AID=68. Accessed March 13, 2023.
79. Sato D, Callegaro D, Lana-Peixoto MA, Fujihara K. Treatment of neuromyelitis optica: an evidence-based review. *Arq Neuropsiquiatr* 2012;70(1):59-66.
80. Corbellino M, Bestetti G, Scalarnogna C, et al. Long-term remission of Kaposi sarcoma-associated herpes virus-related multicentric Castleman disease with anti-CD20 monoclonal antibody therapy. *Blood* 2001;98:3473-3475.
81. Ghazal H. Successful treatment of pure red cell aplasia with rituximab in patients with chronic lymphocytic leukemia. *Blood* 2002;99:1092-1094.
82. Dungarwalla M, Marsh JC, Tooze JA, et al. Lack of clinical efficacy of rituximab in the treatment of autoimmune neutropenia and pure red cell aplasia: implications for their pathophysiology. *Ann Hematol*. 2007 Mar;86(3):191-7. Epub 2006 Nov 23.
83. Wiestner A, Cho HJ, Asch AS, et al. Rituximab in the treatment of acquired factor VIII inhibitors. *Blood* 2002;100:3426-3428.
84. Sperr WR, Lechner K, Pabinger I. Rituximab for the treatment of acquired antibodies to factor VIII. *Haematologica*. 2007 Jan;92(1):66-71.
85. Renaud S, Gregor M, Fuhr P, et al. Rituximab in the treatment of polyneuropathy associated with anti-MAG antibodies. *Muscle Nerve* 2003;27:611-615.
86. Remuzzi G, Chiurciu C, Abbate M, et al. Rituximab for idiopathic membranous nephropathy. *Lancet* 2002;360:923-924.
87. Ruggenenti P, Chiurciu C, Brusegan V, et al. Rituximab in idiopathic membranous nephropathy: A one-year prospective study. *J Am Soc Nephrol* 2003;14:1851-1857.
88. Fervenza FC, Cosio FG, Erickson SB, et al. Rituximab treatment of idiopathic membranous nephropathy. *Kidney Int*. 2008 Jan;73(1):117-25.
89. Ratanatharathorn V, Ayash L, Reynolds C, Silver S, Reddy P, Becker M, Ferrara JL, Uberti JP. Treatment of chronic graft-versus-host disease with anti-CD20 chimeric monoclonal antibody. *Biol Blood Marrow Transplant*. 2003 Aug;9(8):505-11.
90. Zaja F, Bacigalupo A, Patriarca F, et al. Treatment of refractory chronic GVHD with rituximab: a GITMO study. *Bone Marrow Transplant*. 2007 Aug;40(3):273-7.
91. Teshima T, Najafuji K, Henzan H, et al. Rituximab for the treatment of corticosteroid-refractory chronic graft-versus-host disease. *Int J Hematol* 2009;90:253-260.
92. Cutler C, Miklos D, Kim HT, et al. Rituximab for steroid-refractory chronic graft-versus-host disease. *Blood* 2006;108:756-62.
93. Vieira CA, Agarwal A, Book BK, et al. Rituximab for reduction of anti-HLA antibodies in patients awaiting renal transplantation: 1. Safety, pharmacodynamics, and pharmacokinetics. *Transplantation* 2004;77:542-548.
94. Kim S, Kim W, Li XF, et al. Repeated Treatment with Rituximab Based on the Assessment of Peripheral Circulating Memory B Cells in Patients with Relapsing Neuromyelitis Optica Over 2 Years. *Arch Neurol*. 2011;68(11):1412-1420.
95. Scott TF, Frohman EM, DeSeze J, et al. Evidence-based guideline: Clinical evaluation and treatment of transverse myelitis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2011 Dec 13;77(24):2128-34.
96. Chung L, Genovese MC, Fiorentino DF. A pilot trial of rituximab in the treatment of patients with dermatomyositis. *Arch Dermatol*. 2007 Jun;143(6):763-7.

97. Cooper MA, Willingham DL, Brown DE, et al. Rituximab for the treatment of juvenile dermatomyositis: a report of four pediatric patients. *Arthritis Rheum.* 2007 Sep;56(9):3107-11.
98. Mok CC, Ho LY, To CH. Rituximab for refractory polymyositis: an open-label prospective study. *J Rheumatol.* 2007 Sep;34(9):1864-8.
99. Levine TD. Rituximab in the treatment of dermatomyositis: an open-label pilot study. *Arthritis Rheum.* 2005 Feb;52(2):601-7.
100. He D, Guo R, Zhang F, et al. Rituximab for relapsing-remitting multiple sclerosis. *Cochrane Database Syst Rev.* 2013 Dec 6;12:CD009130.
101. Léger JM, Viala K, Nicolas G, et al. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein neuropathy. *Neurology.* 2013 Jun 11;80(24):2217-25.
102. Zara G, Zambello R, Ermani M. Neurophysiological and clinical responses to rituximab in patients with anti-MAG polyneuropathy. *Clin Neurophysiol.* 2011 Dec;122(12):2518-22.
103. FDA Drug Safety Communication: Boxed Warning and new recommendations to decrease risk of hepatitis B reactivation with the immune-suppressing and anti-cancer drugs Arzerra (ofatumumab) and Rituxan (rituximab) <http://www.fda.gov/Drugs/DrugSafety/ucm366406.htm>. Accessed February 4, 2014.
104. Dalakas MC, Rakocevic G, Salajegheh M, et al. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein antibody demyelinating neuropathy. *Ann Neurol.* 2009 Mar;65(3):286-93. doi: 10.1002/ana.21577.
105. Berezne GL, Galicier, A. Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus associated multicentric Castleman's disease: ANRS 117 CastlemaB Trial. *J Clin Oncol* 2007; 25:3350–3356.
106. van Dorp S, Resemann H, te Boome L, Pietersma F, van Baarle D, Gmelig-Meyling F, de Weger R, Petersen E, Minnema M, Lokhorst H, Ebeling S, Beijin SJ, Knol EF, van Dijk M, Meijer E, Kuball J. The immunological phenotype of rituximab-sensitive chronic graft-versus-host disease: a phase II study. *Haematologica.* 2011 Sep;96(9):1380-4.
107. Lopez-Olivo MA, Amezaga Urruela M, McGahan L, Pollono EN, Suarez-Almazor ME. Rituximab for rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2015, Issue 1. Art. No.: CD007356.
108. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Management of Immunotherapy-Related Toxicities, Version 1.2019. Accessed March 13, 2023.
109. Truxima [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; February 2022.
110. Dane K, Chaturvedi S. Beyond plasma exchange: novel therapies for thrombotic thrombocytopenic purpura. *Hematology.* 2018 Nov 30;2018(1):539-547.
111. Froissart A, Buffet M, Veyradier A, et al; Experience of the French Thrombotic Microangiopathies Reference Center. Efficacy and safety of first-line rituximab in severe, acquired thrombotic thrombocytopenic purpura with a suboptimal response to plasma exchange. *Crit Care Med.* 2012;40(1):104-111.
112. Scully M, McDonald V, Cavenagh J, et al. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. *Blood.* 2011;118(7):1746-1753.
113. Ineichen BV, Moridi T, Granbert T, et al. Rituximab treatment for multiple sclerosis. [Mult Scler.](#) 2019 Jun 25:1352458519858604.
114. Granqvist M, Boremalm M, Poorghobad A, et al. Comparative effectiveness of rituximab and other initial treatment choices for multiple sclerosis. *JAMA Neuro* 2018; 75(3):320-327.
115. Castillo-Trivino T, Braithwaite D, Bacchetti P, et al. Rituximab in relapsing and progressive forms of multiple sclerosis: a systematic review. *PloS One.* 2013 Jul 2;8(7):366308.
116. Riabni [prescribing information]. Thousand Oaks, CA: Amgen, Inc.; June 2022.

Policy History/Revision Information

Date	Summary of Changes
06/01/2023	<p>Coverage Rationale</p> <p>General Requirements</p> <ul style="list-style-type: none"> Added language applicable to all medical necessity requests to indicate:

Date	Summary of Changes
	<ul style="list-style-type: none"> ○ For initial therapy, one of the following: <ul style="list-style-type: none"> ▪ Prescriber attests dosing is in accordance with the United States Food and Drug Administration (FDA) approved labeling ▪ For indications without U.S. FDA approved dosing, prescriber attests there is published clinical evidence to support the dosing ○ For continuation of therapy, both of the following: <ul style="list-style-type: none"> ▪ Documentation of a positive clinical response (relocated from <i>Diagnosis-Specific Criteria</i> section of the policy) ▪ One of the following: <ul style="list-style-type: none"> – Prescriber attests dosing is in accordance with the U.S. FDA approved labeling – For indications without U.S. FDA approved dosing, prescriber attests there is published clinical evidence to support the dosing <p>Diagnosis-Specific Criteria</p> <ul style="list-style-type: none"> ● Removed specific dosage requirements for the use of rituximab; refer to the applicable U.S. FDA approved labeling <p>Neuromyelitis Optica</p> <ul style="list-style-type: none"> ● Revised coverage criteria for continuation of therapy; removed criterion requiring: <ul style="list-style-type: none"> ○ Submission of medical records (e.g., chart notes, laboratory tests) to demonstrate a positive clinical response from baseline as demonstrated by at least both of the following: <ul style="list-style-type: none"> ▪ Reduction in the number and/or severity of relapses or signs and symptoms of NMOSD ▪ Maintenance, reduction, or discontinuation of dose(s) of any baseline immunosuppressive therapy (IST) prior to starting rituximab (add on, dose escalation of IST, or additional rescue therapy from baseline to treat NMOSD or exacerbation of symptoms while on rituximab therapy will be considered as treatment failure) ○ Prescribed by or in consultation with a neurologist <p>Rheumatoid Arthritis</p> <ul style="list-style-type: none"> ● Removed reference to medication brand name “Humira” ● Revised coverage criteria for continuation of therapy; removed criterion requiring: <ul style="list-style-type: none"> ○ Patient is receiving concurrent therapy with methotrexate ○ History of contraindication or intolerance to methotrexate <p>Wegener’s Granulomatosis or Microscopic Polyangiitis (Both ANCA-Associated Vasculidities)</p> <ul style="list-style-type: none"> ● Revised coverage criteria for continuation of therapy; removed criterion requiring: <ul style="list-style-type: none"> ○ Patient is receiving concurrent therapy with glucocorticoids ○ History of contraindication or intolerance to glucocorticoids <p>Supporting Information</p> <ul style="list-style-type: none"> ● Updated <i>References</i> section to reflect the most current information ● Archived previous policy version CS2023D0003AJ

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.