Drug and Biologic Coverage Policy

Effective Date 1/15/2024
Next Review Date.....1/15/2025
Coverage Policy Number IP0319

Rituximab for Non-Oncology Indications

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Oncology Medications - 1403

INSTRUCTIONS FOR USE

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

Overview

This policy supports medical necessity review for the following rituximab products for non-oncology indications:

- **Rituxan**® (rituximab intravenous infusion)
- **Riabni**™ (rituximab-arrx intravenous infusion)
- **Ruxience**® (rituximab-pvvr intravenous infusion)
- **Truxima**® (rituximab-abbs intravenous infusion)

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

Additional criteria that support the review for medical necessity exceptions of non-covered/non-preferred products are located in the Non-Covered/Non-Preferred Product Table by the respective plan type and drug list where applicable.

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

Medical Necessity Criteria

Rituximab products (Rituxan, Riabni, Ruxience, Truxima) are considered medically necessary when ONE of the following is met:

1. **Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis.** Individual meets **ONE** of the following criteria:
    A. Induction Treatment. Individual meets **ALL** of the following:
        i. Individual has an ANCA-associated vasculitis
        Note: Examples of ANCA-associated vasculitis include granulomatosis with polyangiitis (GPA) [Wegener's granulomatosis], Churg-Strauss syndrome, microscopic polyangiitis (MPA), or pauci-immune glomerulonephritis.
        ii. The medication is being administered in combination with glucocorticoids unless there is a documented failure, contraindication or intolerance to glucocorticoids
        iii. The medication is prescribed by or in consultation with a rheumatologist, nephrologist, or immunologist
        iv. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)
    B. Follow-Up Treatment of Individuals Who Have Received Induction Treatment for ANCA-Associated Vasculitis. Individual meets **ALL** of the following:
    Note: This includes an individual who received induction treatment using a rituximab product or other standard of care immunosuppressants.
        i. Individual achieved disease control with induction treatment
        ii. At least 16 weeks will elapse between courses of a rituximab product
        iii. The medication is prescribed by or in consultation with a rheumatologist, nephrologist, or immunologist
        iv. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)

    Dosing. ONE of the following:
        1. Initial Therapy: **ONE** of the following:
            A. 375 mg/m^2 per dose administered intravenously for 4 doses separated by at least 7 days
            B. Up to two 1,000 mg intravenous doses separated by at least 2 weeks
        2. Follow-Up Treatment of an Individual Who Has Received Induction Treatment for ANCA-Associated Vasculitis: **ONE** of the following:
            A. 18 years of age or older: Up to 1,000 mg administered by intravenous infusion every 4 to 6 months based on clinical evaluation, for up to 6 doses
            B. Less than 18 Years of age: Two - 250 mg/m^2 intravenous infusions separated by two weeks, followed by a 250 mg/m^2 intravenous infusion every 6 months thereafter based on clinical evaluation
2. **Pemphigus Vulgaris and Other Refractory Autoimmune Blistering Diseases.** Individual meets **ONE** of the following criteria:
    Note: Examples of other autoimmune blistering diseases include pemphigus foliaceus, bullous pemphigoid, cicatricial pemphigoid, epidermolysis bullosa acquisita, and paraneoplastic pemphigus
    A. Initial Treatment. Individual meets **ALL** of the following:
        i. Therapy is initiated in combination with a systemic corticosteroid (for example, prednisone) unless there is a documented failure, contraindication or intolerance to corticosteroids
        ii. The medication is prescribed by or in consultation with a dermatologist
        iii. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)
    B. Individual is Being Treated for a Relapse or for Maintenance of Pemphigus Vulgaris or Other Refractory Autoimmune Blistering Disease. Individual meets **BOTH** of the following:

i. Subsequent infusions will be administered no sooner than 16 weeks following the previous infusion of a rituximab product
ii. The medication is prescribed by or in consultation with a dermatologist
iii. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)

Dosing. ONE of the following:
1. Initial Treatment or Treatment of a Relapse: One course of therapy, which consists of up to two 1,000 mg doses administered as an intravenous infusion separated by at least 2 weeks
2. Maintenance Therapy: Up to 500 mg per dose administered intravenously at month 12 and every 6 months thereafter or based on clinical evaluation

3. **Rheumatoid Arthritis.** Individual meets **ALL** of the following criteria:
   A. 18 years of age or older
   B. The rituximab product will be used in combination with methotrexate unless there is a documented failure, contraindication or intolerance to methotrexate
   C. The medication will not be used concurrently with another biologic or with a targeted synthetic DMARD. Refer to Appendix A for examples of biologics and targeted synthetic DMARDs
   D. Individual meets **ONE** of the following:
      i. Initial Therapy. Individual meets **ALL** of the following:
         a. Documentation of failure (after a minimum 3 month trial) to at least **ONE** conventional synthetic disease-modifying antirheumatic drug (DMARD) (for example, methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine) **OR** has a contraindication, or intolerance to conventional synthetic disease-modifying antirheumatic drugs (DMARDs)[†]
         b. Documentation of failure (after a minimum 3 month trial) to at least **ONE** anti-tumor necrosis factor (TNF) biologic therapy **OR** has a contraindication or intolerance to anti-tumor necrosis factor (TNF) biologic therapy

            [†]Note: An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the individual already has a 3-month trial of at least one biologic or targeted synthetic DMARD. Refer to Appendix A for examples of biologics and tsDMARDs used for rheumatoid arthritis. An individual who has already tried a biologic or tsDMARD is not required to "step back" and try a conventional synthetic DMARD

         c. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)

      ii. Individual has already Received One or More Courses of a Rituximab Product for Rheumatoid Arthritis. Individual meets **ALL** of the following:
         a. 16 weeks or greater will elapse between treatment courses (for example, there will be a minimum of 16 weeks since the first dose of the previous course and the first dose of the next course of a rituximab product)
         b. If the individual has already received two or more courses of therapy, there is documentation of beneficial response
            Examples of a beneficial response include: less joint pain or morning stiffness; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values (for example, CRP, ESR, anemia); reduced dosage of corticosteroids
         c. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)

   E. The medication is prescribed by or in consultation with a rheumatologist.

Dosing. One course of therapy, which consists of up to two 1,000 mg intravenous doses separated by at least 2 weeks

4. **Graft-Versus-Host Disease.** Individual meets **ALL** of the following criteria:
    A. Documentation of failure, contraindication, or intolerance to **ONE** conventional systemic treatment for graft-versus-host disease [for example, systemic corticosteroids (methylprednisolone, prednisone), cyclosporine, tacrolimus, mycophenolate mofetil, Imbruvica (ibrutinib capsules and tablets), imatinib, antithymocyte globulin, Nipent (pentostatin infusion), or an infliximab product]
    B. The medication is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center
    C. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)

    Dosing. Up to 375 mg/m^2 administered intravenously with doses separated by at least 7 days

5. **Immune or Idiopathic Thrombocytopenia (ITP).** Individual meets **ONE** of the following criteria:
    A. Initial Therapy. Individual meets **ALL** of the following:
        i. Documentation of failure, contraindication, or intolerance to **ONE** other therapy for ITP (for example, intravenous immunoglobulin (IVIG), anti-D (RHO) immunoglobulin, corticosteroids, or splenectomy)
        ii. The medication is prescribed by or in consultation with a hematologist
        iii. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)
    B. Individual has Already Received a Course of a Rituximab Product for ITP. Individual meets **ALL** of the following:
        i. At least 6 months will elapse between treatment courses (for example, there will be a minimum of 6 months separating the first dose of the previous course and the first dose of the requested course of a rituximab product)
        ii. Documentation that the individual responded to therapy (for example, a platelet count increase from baseline following treatment with a rituximab product)
        iii. The prescriber has determined that the individual has relapsed (for example, the individual experiences thrombocytopenia after achievement of a remission)
        iv. The medication is prescribed by or in consultation with a hematologist
        v. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)

    Dosing. Up to 375 mg/m^2 administered intravenously with doses separated by at least 7 days

6. **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitors.** Individual meets **ONE** of the following criteria:
    A. Initial Therapy. Individual meets **ALL** of the following:
        i. Is symptomatic despite a trial of at least **ONE** systemic corticosteroid (for example, methylprednisolone or prednisone)
        ii. The medication is prescribed by or in consultation with an oncologist, neurologist, rheumatologist, or dermatologist
        iii. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)
    B. Individual has Already Received a Course of a Rituximab Product. Individual meets **BOTH** of the following:
        i. The medication is prescribed by or in consultation with an oncologist, neurologist, rheumatologist, or dermatologist
        ii. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)

    Dosing. ONE of the following:
        1. Up to 500 mg/m^2 administered intravenously for 2 doses separated by at least 14 days
        2. Up to 375 mg/m^2 administered intravenously for 4 doses separated by at least 7 days

7. **Multiple Sclerosis.** Individual meets **ALL** of the following criteria:
    A. Documentation of failure, contraindication, or intolerance to at least **ONE** other disease-modifying agent for multiple sclerosis

B. The medication will not be used concurrently with another disease-modifying agent used for multiple sclerosis.

   Refer to Appendix B for examples of disease-modifying agents used for multiple sclerosis

C. At least 6 months will elapse between treatment courses (for example, there will be a minimum of 6 months separating the first dose of the previous course and the first dose of the requested course of a rituximab product)
D. The medication is prescribed by or in consultation with a physician who specializes in the treatment of multiple sclerosis and/or a neurologist
E. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)

Dosing. Up to 2,000 mg (total) administered as one or two intravenous infusions administered over 1 month.

8. **Neuromyelitis Optica Spectrum Disorder.** Individual meets **ALL** of the following criteria:
   A. Documented diagnosis of neuromyelitis optica spectrum disorder
   B. The medication is prescribed by or in consultation with a neurologist
   C. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)

   Dosing. ONE of the following:
   1. Up to 375 mg/m^2 administered intravenously for 4 doses separated by at least 7 days
   2. Up to two 1,000 mg doses administered as an intravenous infusion separated by at least 2 weeks

9. **Systemic Lupus Erythematous (SLE) [Lupus].** Individual meets **ONE** of the following criteria: This includes nephrotic syndrome in a patient with SLE.
   A. Initial Therapy. Individual meets **ALL** of the following:
      i. Documentation of failure, contraindication, or intolerance to **ONE** standard immunomodulating or immunosuppressant agent [for example, hydroxychloroquine, corticosteroids (e.g., prednisone, methylprednisolone), methotrexate, azathioprine, mycophenolate, or cyclophosphamide]
      ii. The medication is prescribed by or in consultation with a rheumatologist, nephrologist, or neurologist.
      iii. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)
   B. Individual has Already Received a Course of a Rituximab Product for SLE. Individual meets **ALL** of the following:
      i. At least 6 months will elapse between treatment courses (for example, there will be a minimum of 6 months separating the first dose of the previous course and the first dose of the requested course of a rituximab product)
      ii. The individual has had a documented beneficial response to therapy
          Examples of a beneficial response include: reduction in flares; reduction in corticosteroid dose; decrease of anti-dsDNA titer; improvement in specific organ dysfunction (for example, musculoskeletal, blood, hematologic, vascular, others)
      iii. The medication is prescribed by or in consultation with a rheumatologist, nephrologist, or neurologist.
      iv. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)

10. **Factor Inhibitors in an Individual with Hemophilia.** Individual meets the following criteria:
    A. Refractory to conventional treatments (for example, immune tolerance induction [ITI], steroids, cyclophosphamide)
    B. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)

11. **Membranous Nephropathy/Membranous Glomerular Nephropathy.** Individual meets **ALL** of the following criteria:

A. Individual has **ONE** of the following:
    i. Membranous nephropathy and eGFR < 60 ml/min or declining renal function not otherwise explained
    ii. Membranous nephropathy with nephrotic syndrome (nephrotic proteinuria, peripheral edema, hypoalbuminemia)
    iii. Membranous nephropathy with nephrotic proteinuria (> 3.5 gm/day after 6 months conservative therapy with ACEi or ARB)
    iv. Recurrent membranous nephropathy with proteinuria > 1 gm/day in a kidney transplant recipient
B. The medication is prescribed by or in consultation with a nephrologist
C. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)

12. **Myasthenia Gravis (MG).** Individual meets **BOTH** the following:
    A. Documented failure, contraindication, or intolerance to at least **TWO** immunosuppressive agents (for example, azathioprine, cyclosporine, or methotrexate)
    B. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)

13. **Pediatric Nephrotic Syndrome.** Individual meets **ALL** of the following criteria:
    A. Individual is 18 years of age or younger
    B. Disease is relapsing and steroid-dependent
    C. Documentation of failure, contraindication, or intolerance to corticosteroid or immunosuppressive medication (for example, cyclophosphamide, cyclosporine, mycophenolate mofetil)
    D. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)

14. **Refractory Autoimmune Hemolytic Anemia.** Individual meets **BOTH** of the following criteria:
    A. Documented failure, contraindication, or intolerance to conventional treatments (for example, corticosteroids, immunosuppressants, or immunoglobulin)
    B. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)

15. **Solid Organ Transplant.** Individual meets **BOTH** of the following criteria:
    A. **ONE** of the following:
        i. Desensitization for highly-allosensitized transplant candidates (to reduce HLA antibodies)
        ii. Antibody-mediated rejection (AMR)
    B. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)

16. **Thrombotic Thrombocytopenic Purpura (TTP).** Individual meets **ALL** of the following criteria:
    A. Diagnosis of thrombotic thrombocytopenic purpura
    B. Rituximab will be used in combination with plasma exchange therapy
    C. Individual is receiving concurrent therapy with glucocorticoids unless there is a documented failure, contraindication, or intolerance to glucocorticoids
    D. The medication is prescribed by or in consultation with a hematologist
    E. For Rituxan, Non-Covered/Non-Preferred Product Criteria is met, refer to below table(s)

Employer Group Non-Covered/Non-Preferred Products and Criteria:

Non-Covered/Non-Preferred Product	Criteria
Rituxan (rituximab intravenous infusion)	Documentation of **ONE** of the following: 1. Individual has previously started on or is currently receiving Rituxan (rituximab) 2. Trials of AND cannot continue to use the alternative(s) due to a formulation difference in the inactive ingredient(s) which, according to the prescriber, would result in a significant allergy or serious adverse reaction to **ALL** of the following:

Non-Covered/Non-Preferred Product	Criteria
	A. Riabni (rituximab-arrx) [may require prior authorization] B. Ruxience (rituximab-pvvr) [may require prior authorization] C. Truxima (rituximab-abbs) [may require prior authorization]

Individual and Family Plan Non-Covered/Non-Preferred Products and Criteria:

Non-Covered/Non-Preferred Product	Criteria
Rituxan (rituximab intravenous infusion)	Documentation of **ONE** of the following: 1. Individual has previously started on or is currently receiving Rituxan (rituximab) 2. Trials of AND cannot continue to use the alternative(s) due to a formulation difference in the inactive ingredient(s) which, according to the prescriber, would result in a significant allergy or serious adverse reaction to **ALL** of the following: A. Riabni (rituximab-arrx) [may require prior authorization] B. Ruxience (rituximab-pvvr) [may require prior authorization] C. Truxima (rituximab-abbs) [may require prior authorization]

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

Reauthorization Criteria

Continuation of rituximab products (Rituxan, Riabni, Ruxience, Truxima) are considered medically necessary for **ALL** covered diagnoses when the above medical necessity criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration: up to 12 months
Reauthorization approval duration: up to 12 months

Conditions Not Covered

Rituximab products (Rituxan, Riabni, Ruxience, Truxima) are considered experimental, investigational or unproven for **ANY** other non-oncology use including the following (this list may not be all inclusive):

1. Pediatric Acute-Onset Neuropsychiatric Syndrome/Pediatric Autoimmune Neuropsychiatric Disorders (PANS/PANDAS)
2. Concomitant use with Enspryng™ (satralizumab-mwge subcutaneous injection), Soliris® (eculizumab injection), Ultomiris (ravulizumab intravenous infusion), or Uplizna™ (inebilizumab-cdon intravenous infusion)

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

Coding / Billing Information

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

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J9312	Injection, rituximab, 10 mg
Q5115	Injection, rituximab-abbs, biosimilar, (truxima), 10 mg
Q5119	Injection, rituximab-pvvr, biosimilar, (ruxience), 10 mg
Q5123	Injection, rituximab-arrx, biosimilar, (Riabni), 10 mg

Background

OVERVIEW
Rituximab products are CD20-directed cytolytic antibodies. All approved rituximab intravenous products are indicated for treatment of the following conditions:

- **Chronic lymphocytic leukemia** (CLL), in combination with fludarabine and cyclophosphamide (FC) for the treatment of patients with previously untreated and previously treated CD20-positive disease.
- **Granulomatosis with polyangiitis** (Wegener's granulomatosis) and **microscopic polyangiitis** in adults, in combination with glucocorticoids.
- **Non-Hodgkin lymphoma** (NHL), for the following uses:
  - previously untreated follicular, CD20-positive disease, in combination with first-line chemotherapy, and in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as a single-agent maintenance therapy.
  - for relapsed or refractory, low-grade or follicular, CD20-positive, B-cell disease.
  - for non-progressing (including stable disease) low-grade, CD20-positive, B-cell disease as a single agent after first-line cyclophosphamide/vincristine/prednisone (CVP) chemotherapy.
  - for previously untreated diffuse large B-cell, CD20-positive disease, in combination with cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) or other anthracycline-based chemotherapy regimens.
- **Rheumatoid arthritis**, in adult patients with moderately to severely active disease, in combination with methotrexate for patients who have had an inadequate response to one or more tumor necrosis factor inhibitors (TNFis).

In addition to the above indications, Rituxan intravenous is also indicated for treatment of the following conditions:

- **Granulomatosis with polyangiitis** (Wegener's granulomatosis) and **microscopic polyangiitis** in patients ≥ 2 years of age, in combination with glucocorticoids.
- **Pemphigus vulgaris**, for adults with moderate to severe disease.
- **B-cell lymphoma,** in patients ≥ 6 months of age with previously untreated, advanced stage, CD20-positive diffuse large B-cell lymphoma, Burkitt lymphoma, Burkitt-like lymphoma, or mature B-cell acute leukemia in combination with chemotherapy.

Riabni, Ruxience, and Truxima are approved as biosimilar to Rituxan intravenous, indicating no clinically meaningful differences in safety and effectiveness and the same mechanism of action, route of administration, dosage form, and strength as Rituxan intravenous. However, minor differences in clinically inactive components are allowed. At this time, the biosimilars have only demonstrated biosimilarity, not interchangeability.

Guidelines
The use of rituximab is supported in clinical guidelines in numerous situations, both as first-line therapy and in patients who are refractory or have relapsed following treatment with other therapies.[4-21]

- **Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis:** Guidelines from the American College of Rheumatology (ACR) [2021] list rituximab among the alternatives for induction or maintenance of remission. Various regimens are recommended with a typical maximum of 1,000 mg/infusion. For maintenance dosing, at least 4 months should separate doses. The optimal dose of rituximab for remission maintenance remains uncertain. Although scheduled maintenance is conditionally recommended over use of CD19+ B-cell counts and/or ANCA titers to guide retreatment, there are data to support both approaches.
- **Immune Thrombocytopenia (ITP):** Guidelines from the American Society of Hematology (ASH) for ITP (2019) mention rituximab as an alternative for children and adults with ITP who do not respond to first-line treatment, and for adults who are corticosteroid-dependent.[17]
- **Multiple Sclerosis (MS):** In June 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[18] Rituximab is listed among various options, involving different mechanisms of action and modes of administration, which have shown benefits in patients with MS. The American Academy of Neurology has practice guidelines regarding disease-modifying therapies for adults with MS.[19] The guidelines mention rituximab for use in MS.
- **Neuromyelitis Optica Spectrum Disorders:** A review article lists rituximab as an effective treatment for neuromyelitis optica.[20]
- Oncology indications covered in National Comprehensive Cancer Network (NCCN) guidelines:[6]
    - **Acute Lymphoblastic Leukemia (ALL):** Guidelines (version 1.2022 – April 4, 2022) list rituximab in multiple regimens for Philadelphia chromosome (Ph)-negative disease for patients with CD20-positive disease.[11] In those with Ph-positive disease, rituximab should be considered in addition to chemotherapy for those with CD20-positive disease, especially in those < 60 years of age.
    - **B-Cell Lymphomas:** In the guidelines (version 5.2022 – July 12, 2022), rituximab is included in multiple treatment regimens across the spectrum of disease.[8] Guidelines for pediatric aggressive mature B-cell lymphomas (version 1.2022 – April 11, 2022) include rituximab intravenous as a component of treatment regimens for induction therapy/initial treatment and as subsequent therapy for relapsed or refractory disease.[9] For primary cutaneous B-cell lymphomas (version 2.2022 – June 8, 2022), rituximab is a treatment option for patients with primary cutaneous B-cell lymphoma.[10]
    - **CLL/Small Lymphocytic Lymphoma:** Rituximab features prominently in the guidelines (version 3.2022 – June 3, 2022) and is included in multiple treatment regimens across the spectrum of disease.[7]
    - **Graft-Versus-Host Disease (GVHD):** Guidelines (version 1.2022 – April 1, 2022) list rituximab among the agents used for steroid-refractory chronic GVHD.[15]
    - **Hairy Cell Leukemia:** Guidelines (version 2.2022 – September 8, 2022) recommend rituximab as a component in a preferred primary regimen, and in multiple regimens for relapsed/refractory disease (including in patients with progressive disease after relapsed/refractory therapy).[12]
    - **Hodgkin Lymphoma:** Guidelines (version 2.2022 – February 23, 2022) recommend rituximab ± chemotherapy and/or radiation (depending on the clinical presentation) in the first-line setting for nodular lymphocyte-predominant disease.[13] Rituximab is also used for relapsed/refractory disease and for maintenance. Guidelines for pediatric disease (version 1.2022 – April 8, 2022) include rituximab in regimens for primary treatment of nodular lymphocyte-predominant disease.[25]
    - **Primary Central Nervous System Lymphoma:** Guidelines for central nervous system cancers (version 1.2022 – June 2, 2022) recommend rituximab-containing regimens in multiple regimens for induction therapy and relapsed or refractory primary central nervous system lymphoma.[24]
    - **Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma:** Guidelines (version 1.2023 – July 6, 2022) include rituximab in regimens across the spectrum of disease (primary therapy, previously treated disease, and maintenance).[14]
- **Pemphigus Vulgaris:** British guidelines (2017) list rituximab in combination with corticosteroids as a first-line therapy.[23]
- **Rheumatoid Arthritis:** Guidelines from ACR (2021) recommend addition of a biologic or a targeted synthetic DMARD for a patient taking the maximum tolerated dose of methotrexate who is not at target.[16]
- **Systemic Lupus Erythematous (SLE):** European League Against Rheumatism (EULAR) recommendations for the management of SLE (2019) mention rituximab as a therapeutic option for patients who are refractory to standard immunosuppressive therapies.[21]

APPENDIX A

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzaa SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	RA
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; ^ Off-label use of Kineret in JIA supported in guidelines; DMARDs – Disease-modifying antirheumatic drug.

APPENDIX B

Disease-Modifying Agents Used for Multiple Sclerosis	Mode of Administration
Aubagio® (teriflunomide tablets)	Oral
Avonex® (interferon beta-1a intramuscular injection)	Injection (self-administered)
Bafiertam® (monomethyl fumarate delayed-release capsules)	Oral
Betaseron® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Briumvi™ (ublituximab-xiij intravenous infusion)	Injection
Copaxone® (glatiramer acetate subcutaneous injection, generic)	Injection (self-administered)

Extavia® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Gilenya® (fingolimod capsules)	Oral
Glatopa® (glatiramer acetate subcutaneous injection)	Injection (self-administered)
Kesimpta® (ofatumumab subcutaneous injection)	Injection (self-administered)
Lemtrada® (alemtuzumab intravenous infusion)	Intravenous infusion
Mavenclad® (cladribine tablets)	Oral
Mayzent® (siponimod tablets)	Oral
Ocrevus® (ocrelizumab intravenous infusion)	Intravenous infusion
Plegridy® (peginterferon beta-1a subcutaneous or intramuscular injection)	Injection (self-administered)
Ponvory™ (ponesimod tablets)	Oral
Rebif® (interferon beta-1a subcutaneous injection)	Injection (self-administered)
Tascenso ODT™ (fingolimod orally disintegrating tablets)	Oral
Tecfidera® (dimethyl fumarate delayed-release capsules, generic)	Oral
Tysabri® (natalizumab intravenous infusion)	Intravenous infusion
Vumerity® (diroximel fumarate delayed-release capsules)	Oral
Zeposia® (ozanimod capsules)	Oral

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