Effective Date 7/15/2022
Next Review Date… 7/15/2023
Coverage Policy Number IP0319

Rituximab for Non-Oncology Indications

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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).

Medical Necessity Criteria

Rituximab products (Rituxan, Riabni, Ruxience, Truxima) are considered medically necessary when ONE of the following is met (1 through 15):

1. **Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis.** Individual meets **ONE** of the following criteria (A or B)
    A. Induction Treatment. Individual meets **ALL** of the following (i, ii, and iii):
        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 contraindicated per FDA label, has significant intolerance, or is not a candidate* for glucocorticoids
        iii. The medication is prescribed by or in consultation with a rheumatologist, nephrologist, or immunologist
    B. Follow-Up Treatment of Individuals Who Have Received Induction Treatment for ANCA-Associated Vasculitis. Individual meets **ALL** of the following (i, ii, and iii):
    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

2. **Pemphigus Vulgaris and Other Refractory Autoimmune Blistering Diseases.** Individual meets **ONE** of the following criteria (A or B):
    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 **BOTH** of the following (i and ii)
        i. Therapy is initiated in combination with a systemic corticosteroid (for example, prednisone) unless contraindicated per FDA label, has significant intolerance, or is not a candidate* for corticosteroids
        ii. The medication is prescribed by or in consultation with a dermatologist
    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 and ii):
        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

3. **Rheumatoid Arthritis.** Individual meets **ALL** of the following criteria (A, B, C, D, and E):
    A. Individual is 18 years of age or older
    B. The rituximab product will be used in combination with methotrexate unless contraindicated per FDA label or documented intolerance
    C. The medication will not be used concurrently with another biologic or with a targeted synthetic DMARD
    Note: Refer to Appendix for examples of biologics and targeted synthetic DMARDs
    D. Individual meets **ONE** of the following (i or ii):
        i. Initial Therapy. Individual meets **BOTH** of the following (a and b):
            a. Documentation individual has had an inadequate response (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 per FDA label, significant intolerance, or is

not a candidate* for conventional synthetic disease-modifying antirheumatic drugs (DMARDs)[†]

b. Documentation individual has had an inadequate response (after a minimum 3 month trial) to at least **ONE** anti-tumor necrosis factor (TNF) biologic therapy **OR** has a contraindication per FDA label, significant intolerance, or is not a candidate* for 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 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*

ii. Individual has already Received One or More Courses of a Rituximab Product for Rheumatoid Arthritis. Individual meets **BOTH** of the following (a and b):
   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
   Note: 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

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

4. **Graft-Versus-Host Disease.** Individual meets **BOTH** of the following criteria (A and B):
   A. Documentation of **ONE** of the following (i or ii):
      i. Individual has had an inadequate response 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]
      ii. Individual has a contraindication per FDA label, significant intolerance, or is not a candidate* for conventional systemic treatments for graft-versus-host disease.
   B. The medication is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center

5. **Immune or Idiopathic Thrombocytopenia (ITP).** Individual meets **ONE** of the following criteria (A or B):
   A. Initial Therapy. Individual meets **BOTH** of the following (i and ii):
      i. Documentation of **ONE** of the following (i or ii)
         a. Individual has had an inadequate response to **ONE** other therapy for ITP (for example, intravenous immunoglobulin (IVIG), anti-D (RHO) immunoglobulin, corticosteroids, or splenectomy)
         b. Individual has a contraindication per FDA label, significant intolerance, or is not a candidate* for other therapies for ITP
      ii. The medication is prescribed by or in consultation with a hematologist
   B. Individual has Already Received a Course of a Rituximab Product for ITP. Individual meets **ALL** of the following (i, ii, iii, and iv):
      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

6. **Multiple Sclerosis.** Individual meets **ALL** of the following criteria (A, B, C, and D):
   A. Documentation of **ONE** of the following (i or ii)
      i. Individual has had an inadequate response to at least **ONE** other disease-modifying agent for multiple sclerosis±
      ii. Individual has a contraindication per FDA label, significant intolerance, or is not a candidate* for other disease modifying agents for multiple sclerosis±
   B. The medication will not be used concurrently with another disease-modifying agent used for multiple sclerosis±

      ±Note: Examples of disease-modifying agents for multiple sclerosis include, Ocrevus (ocrelizumab intravenous infusion), Avonex (interferon beta-1a intramuscular injection), Rebif (interferon beta-1a subcutaneous injection), Betaseron (interferon beta-1b subcutaneous injection), Extavia (interferon beta-1b subcutaneous injection), Copaxone (glatiramer acetate subcutaneous injection), Glatopa (glatiramer acetate subcutaneous injection), Plegridy (peginterferon beta-1a subcutaneous injection), Gilenya (fingolimod capsules), Aubagio (teriflunomide tablets), dimethyl fumarate delayed-release capsules, Ponvory (ponesimod tablets), or Lemtrada (alemtuzumab intravenous infusion), Tysabri (natalizumab intravenous infusion), Mavenclad (cladribine tablets), Kesimpta (ofatumumab subcutaneous injection), Vumerity (diroximel fumarate delayed-release capsules), Zeposia (ozanimod capsules), Ocrevus (ocrelizumab intravenous infusion), Bafiertam (monomethyl fumarate delayed-release capsules), or Mayzent (siponimod tablets)

   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

7. **Neuromyelitis Optica Spectrum Disorder.** Individual meets **BOTH** of the following criteria (A and B):
   A. Documented diagnosis of neuromyelitis optica spectrum disorder
   B. The medication is prescribed by or in consultation with a neurologist

8. **Systemic Lupus Erythematous (SLE) [Lupus].** Individual meets **ONE** of the following criteria (A or B):
   Note: This includes nephrotic syndrome in a patient with SLE.
   A. Initial Therapy. Individual meets **BOTH** of the following (i and ii)
      i. Documentation of **ONE** of the following (a or b):
         a. Individual has had an inadequate response to **ONE** standard immunomodulating or immunosuppressant agent [for example, hydroxychloroquine, corticosteroids (e.g., prednisone, methylprednisolone), methotrexate, azathioprine, mycophenolate, or cyclophosphamide]
         b. Individual has a contraindication per FDA label, significant intolerance, or is not a candidate* for at least **ONE** standard immunomodulating or immunosuppressant agent
      ii. The medication is prescribed by or in consultation with a rheumatologist, nephrologist, or neurologist.
   B. Individual has Already Received a Course of a Rituximab Product for SLE. Individual meets **ALL** of the following (i, ii, and iii):
      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
         Note: 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.

9. **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)

10. **Membranous Nephropathy/Membranous Glomerular Nephropathy.** Individual meets **BOTH** of the following criteria (A and B):
    A. Individual has **ONE** of the following (i, ii, iii or iv):
       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

11. **Myasthenia Gravis (MG).** Individual meets **ONE** of the following (A or B):
    A. Individual has had an inadequate response to at least **TWO** immunosuppressive agents (for example, azathioprine, cyclosporine, or methotrexate)
    B. Individual has a contraindication per FDA label, significant intolerance, or is not a candidate* for immunosuppressive agents.

12. **Pediatric Nephrotic Syndrome.** Individual meets **ALL** of the following criteria (A, B, and C):
    A. Individual is 18 years of age or younger
    B. Disease is relapsing and steroid-dependent
    C. Documentation of **ONE** of the following (i or ii):
       i. Individual has had an inadequate response to corticosteroid or immunosuppressive medication (for example, cyclophosphamide, cyclosporine, mycophenolate mofetil)
       ii. Individual has a contraindication per FDA label, significant intolerance, or is not a candidate* for corticosteroid or immunosuppressive medication.

13. **Refractory Autoimmune Hemolytic Anemia.** Individual meets the following criteria:
    A. Autoimmune hemolytic anemia that is refractory to conventional treatments (for example, corticosteroids, immunosuppressants, immunoglobulin)

14. **Solid Organ Transplant.** Individual meets **ONE** of the following criteria (A or B):
    A. Desensitization for highly-allosensitized transplant candidates (to reduce HLA antibodies)
    B. Antibody-mediated rejection (AMR)

15. **Thrombotic Thrombocytopenic Purpura (TTP).** Individual meets **ALL** of the following criteria (A, B, C, and D):
    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 contraindicated per FDA label, has significant intolerance, or is not a candidate* for glucocorticoids
    D. The medication is prescribed by or in consultation with a hematologist

**Note: Not a candidate due to being subject to a warning per the prescribing information (labeling), having a disease characteristic, individual clinical factor[s], or other attributes/conditions or is unable to administer and requires this dosage formulation.*

Coverage for rituximab products varies across plans and may require the use of preferred products in addition to the medical necessity criteria listed above. Refer to the customer's benefit plan document for coverage details.

When coverage requires the use of preferred products, there is documentation of **ONE** of the following (A or B):

A. The individual has had inadequate efficacy to the number of covered alternatives according to the table below.
B. The individual has a contraindication according to FDA label, significant intolerance, or is not a candidate* for the covered alternatives according to the table below.

**Note: Not a candidate due to being subject to a warning per the prescribing information (labeling), having a disease characteristic, individual clinical factor[s], other attributes/conditions, or is unable to administer and requires this dosage formulation*

Employer Group Non-Covered Products and Preferred Covered Alternatives by Drug List:

Non-Covered Product	Standard / Performance	Value / Advantage	Cigna Total Savings	Legacy
Rituxan (rituximab intravenous infusion)	**ONE** of the following: • Individual has previously started on or is currently receiving Rituxan (rituximab) **OR** • Individual has documented trials of **ALL** of the following:* ▪ Riabni (rituximab-arrx) ▪ Ruxience (rituximab-pvvr) ▪ Truxima (rituximab-abbs)			

**Prior authorization may apply*

Individual and Family Plan Covered Alternatives:

Non-Covered Product	Covered Alternative(s)
Rituxan (rituximab intravenous infusion)	**ONE** of the following: • Individual has previously started on or is currently receiving Rituxan (rituximab) **OR** • Individual has documented trials of **ALL** of the following:* ▪ Riabni (rituximab-arrx) ▪ Ruxience (rituximab-pvvr) ▪ Truxima (rituximab-abbs)

**Prior authorization may apply*

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.

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

Reauthorization Criteria

Rituximab products (Rituxan, Riabni, Ruxience, Truxima) are considered medically necessary for continued use when initial 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:[1-3,22]

- **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.

In addition to the above indications, Rituxan intravenous and Truxima are also indicated for treatment of the following condition:[1,3]

- **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:[1]

- **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.

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.

FDA Recommended Dosing and Availability

Non–Hodgkin's Lymphoma (NHL)

The recommended dose is 375 mg/m^2 as an intravenous infusion according to the following schedules:

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

Chronic Lymphocytic Leukemia (CLL)

- The recommended dose is 375 mg/m^2 the day prior to the initiation of FC chemotherapy, then 500 mg/m^2 on Day 1 of cycles 2−6 (every 28 days).

Recommended Dose as a Component of Zevalin® for treatment of NHL

- Infuse rituximab 250 mg/m2 within 4 hours prior to the administration of Indium-111-(In-111-) Zevalin and within 4 hours prior to the administration of Yttrium-90-(Y-90-) Zevalin. Administer Rituxan and In-111-Zevalin 7−9 days prior to Rituxan and Y-90-Zevalin. Refer to the Zevalin package insert for full prescribing information regarding the Zevalin therapeutic regimen.

Rheumatoid Arthritis (RA)

- Administer Rituxan as two 1000 mg intravenous infusions separated by 2 weeks. Glucocorticoids administered as methylprednisolone 100 mg intravenous or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion reactions.
- Subsequent courses should be administered every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks. Rituxan is given in combination with methotrexate.

Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)

Induction Treatment of Patients with Active GPA/MPA

- Administer Rituxan as a 375 mg/m^2 intravenous infusion once weekly for 4 weeks for patients with active GPA or MPA.
- Glucocorticoids administered as methylprednisolone 1000 mg intravenously per day for 1 to 3 days followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day and tapered per clinical need) are recommended to treat severe vasculitis symptoms. This regimen should begin within 14 days prior to or with the initiation of Rituxan and may continue during and after the 4 week induction course of Rituxan treatment.

Follow up Treatment of Patients with GPA/MPA who have achieved disease control with induction treatment

- Administer Rituxan as two 500 mg intravenous infusions separated by two weeks, followed by a 500 mg intravenous infusion every 6 months thereafter based on clinical evaluation.
- Patients should receive 100 mg intravenous methylprednisolone to be completed 30 minutes prior to each Rituxan infusion.
- If induction treatment of active disease was with Rituxan, follow up treatment with Rituxan should be initiated within 24 weeks after the last Rituxan induction infusion or based on clinical evaluation, but no sooner than 16 weeks after the last Rituxan induction infusion.
- If induction treatment of active disease was with other standard of care immunosuppressants, Rituxan follow up treatment should be initiated within the 4 week period that follows achievement of disease control.

Pemphigus Vulgaris (PV)

- Administer Rituxan as a two 1000 mg intravenous infusions separated by 2 weeks in combination with a tapering course of glucocorticoids.
- Maintenance treatment- administer as a 500 mg intravenous infusion at month 12 and every 6 months thereafter or based on clinical evaluation.
- Treatment of relapse- administer as a 1000 mg intravenous infusion on relapse, and consider resuming or increasing the glucocorticoid dose based on clinical evaluation.

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

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]

- **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.
- **Myasthenia Gravis (MG):** In 2020, the International Consensus Guidance for Management of Myasthenia Gravis was updated and includes the following recommendations pertaining to rituximab:
  - Rituximab should be considered as an early therapeutic option in patients with MuSK-Ab+ (muscle specific kinase-positive) MG who have an unsatisfactory response to initial immunotherapy.
  - The efficacy of rituximab in refractory AChR-Ab+ (acetylcholine receptor-positive) MG is uncertain. It is an option if patients fail or do not tolerate other immunosuppressive agents.[24]
- **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 1.2021 – April 6, 2021) list rituximab in multiple regimens for Philadelphia chromosome (Ph)-negative 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 4.2021 – May 5, 2021), rituximab is included in multiple treatment regimens across the spectrum of disease.[8] Guidelines for pediatric aggressive mature B-cell lymphomas (version 2.2021 – June 7, 2021) 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 2.2021 – March 4, 2021), 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 4.2021 – April 29, 2021) and is included in multiple treatment regimens across the spectrum of disease.[7]
    - **Graft-Versus-Host Disease (GVHD):** Guidelines (version 2.2021 – April 21, 2021) list rituximab among the agents used for steroid-refractory chronic GVHD.[15]
    - **Hairy Cell Leukemia:** Guidelines (version 2.2021 – March 11, 2021) 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 Disease:** Guidelines (version 4.2021 – April 20, 2021) 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.
    - **Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma:** Guidelines (version 1.2020 – September 1, 2020) 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 the American College of Rheumatology (ACR) [2015] have tumor necrosis factor (TNF) inhibitors and non-TNF biologics (including rituximab), equally positioned following a trial of a conventional synthetic disease-modifying antirheumatic drug (DMARD).[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]
- **Vasculitis:** EULAR and European Renal Association/European Dialysis and Transplant Association (ERA-EDTA) recommendations for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis mention rituximab in combination with low-dose corticosteroids as a potential treatment option for remission-maintenance therapy.[4] Remission-maintenance therapy is recommended for at least 24 months following induction of sustained remission. British guidelines for use of rituximab in ANCA-associated vasculitis recommend rituximab for maintenance of remission to reduce the risk of relapse and its consequences.[5]

APPENDIX

	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.

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