Utilization Review Policy 216B

POLICY: Biosimilars - Rituxan

- Rituxan® (rituximab injection for intravenous use – Genentech)
- Riabni™ (rituximab-arrx for intravenous use – Amgen)

EFFECTIVE DATE: 1/1/2020
LAST REVISION DATE: 09/26/2023

COVERAGE CRITERIA FOR: UCare Medicare Plans Only (UCare Medicare, UCare Medicare with M Health Fairview and North Memorial, EssentiaCare, Group Plans, MSHO, Connect + Medicare, UCare Your Choice)

OVERVIEW

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

1. **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.
2. **Granulomatosis with polyangiitis** (Wegener's granulomatosis) and **microscopic polyangiitis** in adults, in combination with glucocorticoids.
3. **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.
1. **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.
2. **Pemphigus vulgaris**, for adults with moderate to severe disease.
3. **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 2.2023 – July 28, 2023) 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 5.2023 – July 07, 2023), rituximab is included in multiple treatment regimens across the spectrum of disease.[8] Guidelines for pediatric aggressive mature B-cell lymphomas (version 1.2023 – April 04, 2023) 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 lymphomas (version 1.2023 – January 5, 2023), 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 3.2023 – June 12, 2023) and is included in multiple treatment regimens across the spectrum of disease.[7]
    - **Graft-Versus-Host Disease (GVHD):** The hematopoietic cell transplantation guidelines (version 1.2023 – March 31, 2023) list rituximab among the agents used for steroid-refractory chronic GVHD.[15]
    - **Hairy Cell Leukemia:** Guidelines (version 1.2023 – August 30, 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 2.2023 – November 8, 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 2.2023 – March 9, 2023) 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 1.2023 – March 24, 2023) recommend rituximab 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]
- **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitors:** NCCN (version 2.2023 – May 9, 2023) and the American Society of Clinical Oncology (ASCO) guidelines (2021) recommend rituximab as an option for corticosteroid-refractory dermatologic and hematologic immune mediated adverse events, as well as for immune-mediated encephalitis and myositis.[42,43]
- **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 Erythematosus (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]

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of rituximab IV products. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

This policy incorporates Medicare coverage guidance as set forth in National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs), as well as in companion policy articles and other guidance applicable to the relevant service areas. These documents are cited in the References section of this policy. In some cases, this guidance includes specific lists of HCPCS and ICD-10 codes to help inform the coverage determination process. The Articles that include specific lists for billing and coding purposes will be included in the Reference section of this policy. However, to the extent that this policy cites such lists of HCPCS and ICD-10 codes, they should be used for reference purposes only. The presence of a specific HCPCS or ICD-10 code in a chart or companion article to an LCD is not by itself sufficient to approve coverage. Similarly, the absence of such a code does not necessarily mean that the applicable condition or diagnosis is excluded from coverage.

Note: Conditions for coverage outlined in this Medicare Advantage Medical Policy may be less restrictive than those found in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles. Examples of situations where this clinical policy may be less restrictive include, but are not limited to, coverage of additional indications supported by CMS-approved compendia and the exclusion from this policy of additional coverage criteria requirements outlined in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rituxan and Riabni is recommended for requests meeting both the biosimilar step therapy requirements and indication requirements.

Biosimilar Step Therapy Requirements (New Starts Only)

Criteria. *The patient must meet the following criteria (A or B):*

A) For patients new to Rituxan and Riabni only, must have a trial of Truxima or Ruxience prior to approval of Rituxan or Riabni. New starts to therapy defined as no use of Rituxan and Riabni within the past 365 days for Medicare patients.

B) Patient has a contraindication or other clinical reason why a biosimilar cannot be tried before Rituxan or Riabni.

Note: Biosimilar step only required for indications FDA-Approved for both Rituxan and Riabni and the biosimilar(s).

FDA-Approved Indications

1. Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis.

Criteria. *Patient must meet the following criteria (A or B)*:

A) Induction Treatment. Approve for 1 month if the patient meets ALL of the following (i and ii):

- **i.** The patient has an ANCA-associated vasculotide
  Note: Examples of ANCA-associated vasculitis include granulomatosis with polyangiitis [GPA] {Wegener's granulomatosis (WG)} or microscopic polyangiitis [MPA]); AND
- **ii.** The requested agent is being administered in combination with glucocorticoids.

B) Follow-Up Treatment of Patients Who Have Received Induction Treatment for ANCA-Associated Vasculitis (Note: This includes patients who received induction treatment using rituximab infusion or other standard of care immunosuppressants). Approve for 1 year if the patient meets BOTH of the following (i and ii):

- **i.** According to the prescriber, the patient achieved disease control with induction treatment; AND
- **ii.** If the patient previously received a course of therapy, at least 16 weeks will elapse between courses.

Dosing. Approve one of the following (A or B):

A) Initial Therapy: Approve one of the following:

i. 375 mg/m^2 per dose administered intravenously for 4 doses separated by at least 7 days; OR
ii. Up to two 1,000-mg intravenous doses separated by at least 2 weeks.

B) Follow-Up Treatment of a Patient Who Has Received Induction Treatment for ANCA-Associated Vasculitis: Approve one of the following (i or ii):

- **i.** ≥ 18 years of age: Up to 1,000 mg administered by intravenous infusion for 6 doses; OR
- **ii.** < 18 Years of age: Up to 250 mg/m^2 administered by intravenous infusion for 2 doses.

2. Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma.

Criteria. Approve for 1 year.

Dosing. Approve up to 500 mg/m^2 administered as an intravenous infusion on 1 day of each cycle.

3. B-Cell Lymphoma (Note: Examples of B-cell lymphomas include follicular lymphoma, diffuse large B-cell lymphoma, high-grade B-cell lymphoma, acquired immune deficiency (AIDS)-related B-cell lymphoma, Burkitt lymphoma, Castleman's disease, marginal zone lymphoma (e.g., extranodal or MALT [gastric or nongastric], nodal, or splenic marginal zone lymphoma), primary mediastinal large B-cell lymphoma, mantle cell lymphoma, post-transplant lymphoproliferative disorders, gray zone lymphoma, primary cutaneous B-cell lymphoma, pediatric aggressive mature B-cell lymphomas.).

Criteria. Approve for 1 year.

Dosing. Approve one of the following regimens (A or B):
A) Approve up to 375 mg/m^2 per dose administered intravenously with doses separated by at least 7 days; OR
B) Approve up to 375 mg/kg^2 on two days of each cycle.

4. Pemphigus Vulgaris. ^

Criteria. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Treatment. Approve for 1 month.
B) Patient is Being Treated for a Relapse or for Maintenance of Pemphigus Vulgaris. Approve for 1 year if subsequent infusions will be administered no sooner than 16 weeks following the previous infusion of a rituximab product.

Dosing. Approve the following (A or B):
A) Initial Treatment or Treatment of a Relapse: Approve 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; OR
B) Maintenance Therapy: Approve up to 500 mg per dose administered intravenously.

5. Rheumatoid Arthritis (RA). ^

Criteria. Approve if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 1 month (which is adequate duration to administer one course of therapy) if the patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months
Note: Examples of conventional synthetic DMARDs include methotrexate [oral or injectable], leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient already has a 3-month trial of at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix A for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic is not required to "step back" and try a conventional synthetic DMARD.
B) Patient has already Received One or More Courses of Rituximab for Rheumatoid Arthritis (RA). Approve for 1 month (which is adequate duration to administer one course of therapy) if the patient meets BOTH of the following conditions (i and ii):
i. 16 weeks or greater will elapse between treatment courses.
Note: 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; AND
ii. If the patient has already received two or more courses of therapy, the patient meets at least ONE of the following (a or b):

1. Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
   Note: Examples of standardized and validated measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).
2. Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

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

OTHER USES WITH SUPPORTIVE EVIDENCE

6. Acute Lymphoblastic Leukemia.

Criteria. Approve for 1 year if the patient has CD20-positive disease.

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

7. Graft Versus Host Disease.

Criteria. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month if the patient has tried at least one conventional systemic treatment for graft versus host disease; OR
Note: Examples include systemic corticosteroids (methylprednisolone, prednisone), cyclosporine, tacrolimus, mycophenolate mofetil, Imbruvica (ibrutinib capsules and tablets), imatinib, antithymocyte globulin, Nipent (pentostatin infusion), or an infliximab product.

B) Patient has Already Received a Course of a Rituximab Product for Graft-Versus-Host Disease. Approve for 1 year if the patient meets at least ONE of the following (i or ii):

- **i.** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating a rituximab product); OR
  Note: An example of objective measures is normalization of liver function tests, red blood cell count, or platelet count, or resolution of fever or rash.
- **ii.** Compared with baseline (prior to initiating a rituximab product), patient experienced an improvement in at least one symptom, such as improvement in skin, oral mucosal, ocular, or gastrointestinal symptoms (e.g., nausea, vomiting, anorexia).

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

8. Hairy Cell Leukemia.

Criteria. Approve for 1 year.

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

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9. Hodgkin Lymphoma.

Criteria. Approve for 1 year if the patient has nodular lymphocyte-predominant disease.

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

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10. Immune Thrombocytopenia (ITP). ^

Criteria. Approve if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month if the patient has tried one other therapy.
Note: Examples of therapies for ITP include intravenous immunoglobulin (IVIG), anti-D (RHO) immunoglobulin, corticosteroids, and splenectomy.

B) Patient has Already Received a Course of a Rituximab Product for ITP. Approve for 1 month if the patient meets ALL of the following (i, ii, and iii):

- **i.** At least 6 months will elapse between treatment courses
  Note: 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; AND
- **ii.** The patient responded to therapy, as determined by the prescriber.
  Note: Examples of a response include a platelet count increase from baseline following treatment with a rituximab product; AND
- **iii.** The prescriber has determined that the patient has relapsed.
  Note: Examples of a relapse include the patient experiences thrombocytopenia after achievement of a remission.

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

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11. Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitors. ^

Criteria. Approve for the duration noted if the patient meets the following (A or B):
Note: Examples of checkpoint inhibitors are Keytruda (pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), Yervoy (ipilimumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion), Bavencio (avelumab intravenous infusion), Imfinzi (durvalumab intravenous infusion), and Libtayo (cemiplimab-rwlc intravenous infusion).

A) Initial Therapy. Approve for 1 month if the patient is symptomatic despite a trial of at least ONE systemic corticosteroid.
Note: Examples of a corticosteroid include methylprednisolone and prednisone.

B) Patient has Already Received a Course of a Rituximab Product. Approve for 1 month.

Dosing. Approve dosing that meets the following (A or B):

A) Approve up to 500 mg/m^2 administered intravenously for 2 doses separated by at least 14 days; OR

B) Approve up to 375 mg/m^2 administered intravenously for 4 doses separated by at least 7 days.

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12. Multiple Sclerosis. ^

Criteria. Approve for 1 year if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve if the patient meets ALL the following (i and ii):
- a. According to the prescriber, the patient has experienced inadequate efficacy or significant intolerance to at least ONE other disease-modifying agent for multiple sclerosis; AND
  Note: See Appendix B for examples of disease-modifying agents used for multiple sclerosis.
- b. At least 6 months will elapse between treatment courses.
  Note: For example, if the patient has already received a course of therapy 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 therapy.

B) Patient is Currently Receiving Rituximab. Approve if the patient meets one of the following criteria (i or ii):
- a. Patient has been receiving Rituximab for < 1 year. Approve if at least 6 months will elapse between treatment courses; OR
  Note: For example, if the patient has already received a course of therapy 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 therapy.
- b. Patient has been receiving Rituximab for 1 year or more. Approve for 1 year if the patient meets ALL of the following (a and b):
  - i. At least 6 months will elapse between treatment courses; AND
    Note: For example, if the patient has already received a course of therapy 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 therapy.
  - ii. Patient meets ONE of the following [(1) or (2)]:
    1. Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
       Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability Status Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Items Multiple Sclerosis Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and or attenuation of brain volume loss.
    2. Patient experienced stabilization, slow progression, or improvement in at least one symptoms such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation.

Dosing. Approve the following (A and B):

A) Each course is up to 2,000 mg (total); AND
B) Each course is administered as one or two intravenous infusions administered over 1 month.

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13. Neuromyelitis Optica (NMO) Spectrum Disorder.

Criteria. Approve for 1 month.

Dosing. Approve ONE of the following (A or B):
A) Up to 375 mg/m^2 administered intravenously for 4 doses separated by at least 7 days; OR
B) Up to two 1,000-mg doses administered as an intravenous infusion separated by at least 2 weeks.

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14. Primary Central Nervous System Lymphoma.

Criteria. Approve for 1 year.

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

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15. Systemic Lupus Erythematous (SLE) [Lupus].

Criteria. Approve for the duration noted if the patient meets ONE of the following (A or B):
Note: This includes nephrotic syndrome in a patient with SLE.
A) Initial Therapy. Approve for 1 month (adequate duration to receive one course) if the patient has has tried at least ONE standard immunomodulating or immunosuppressant agent
Note: Examples of standard immunomodulating or immunosuppressant agents include hydroxychloroquine, corticosteroids (e.g., prednisone, methylprednisolone), methotrexate, azathioprine, mycophenolate, and cyclophosphamide.
B) Patient has Already Received a Course of a Rituximab Product for SLE. Approve for 1 month (adequate duration to receive one course) if 6 months or greater will elapse between treatment courses (i.e., there will be a minimum of 6 months separating the first dose of the previous rituximab course and the first dose of the requested course of rituximab).

Dosing. Approve the requested dose.

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16. Waldenstrom's Macroglobulinemia/Lymphoplasmacytic Lymphoma.

Criteria. Approve for 1 year.

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

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17. Antibody-Mediated Rejection (AMR).[27]

Criteria.[27] Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 1 month if the patient meets ONE of the following (i or ii):
- **i.** The requested medication is being used as second-line treatment or as part of a combination treatment for AMR in a kidney, lung, or cardiac transplant patient; OR
- **ii.** The requested medication is being used as part of a desensitization protocol in a highly sensitized patient awaiting donor transplant.

B) Patient has Already Received a Course of a Rituximab Product for Antibody-Mediated Rejection. Approve for 1 month if the patient has had a positive response to a previous course of a rituximab product for antibody-mediated rejection.

Dosing.[28-29] Approve ONE of the following (A or B):
A) Up to 375 mg/m^2 administered intravenously with doses separated by at least 7 days; OR
B) Up to two 1,000-mg doses administered as an intravenous infusion separated by at least 2 weeks.

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18. Immune-Mediated Myopathy/Idiopathic Inflammatory Myopathy.[27] (Note: Examples include dermatomyositis, polymyositis, antisynthetase syndrome, immune-mediated necrotizing myopathy, inclusion body myositis, nonspecific myositis).

Criteria.[27] Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 1 month if the patient has refractory disease and has failed all first-line therapies.
B) Patient has Already Received a Course of a Rituximab Product for Immune-Mediated Myopathy/Idiopathic Inflammatory Myopathy. Approve for 1 month if the patient has had a positive response to a previous course of a rituximab product for immune-mediated myopathy/idiopathic inflammatory myopathy.

Dosing.[30-33] Approve ONE of the following (A or B):
A) Up to 375 mg/m^2 administered intravenously with doses separated by at least 7 days; OR
B) Up to two 1,000-mg doses administered as an intravenous infusion separated by at least 2 weeks.

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19. Hemophilia (Acquired).[27]

Criteria. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 1 month if the patient meets ONE of the following (i or ii):
- **i.** The patient has acquired or refractory hemophilia and the requested medication is being used as first-line therapy in combination with corticosteroids; OR
- **ii.** The patient has refractory disease and the requested medication is being used as a second-line agent.

B) Patient has Already Received a Course of a Rituximab Product for Hemophilia (Acquired). Approve for 1 month if the patient has had a positive response to a previous course of a rituximab product for hemophilia (acquired).

Dosing.[34] Approve up to 375 mg/m^2 administered intravenously with doses separated by at least 7 days.

20. Thrombotic Thrombocytopenic Purpura (Acquired).[27]

Criteria.[27] Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 1 month if the patient meets BOTH of the following (i and ii):
- **i.** The patient has severe, relapsed, or refractory disease; AND
- **ii.** The patient has failed first-line therapy (i.e., plasma exchange and glucocorticoids).

B) Patient has Already Received a Course of a Rituximab Product for Thrombotic Thrombocytopenic Purpura (Acquired). Approve for 1 month if the patient has had a positive response to a previous course of a rituximab product for thrombotic thrombocytopenic purpura (acquired).

Dosing.[34-35] Approve ONE of the following (A or B):
A) Approve up to 375 mg/m^2 administered intravenously with doses separated by at least 7 days; OR
B) Approve 100 mg administered intravenously with doses separated by at least 5 days.

21. Immunoglobulin G4-Related Disease (IgG4-RD).[27]

Criteria.[27] Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 1 month if the patient meets ONE of the following (i or ii):
- **i.** The patient has refractory or relapsed disease and the requested medication is being used as second-line therapy after failure of all first-line therapies; OR
- **ii.** The patient has an absolute contraindication to glucocorticoid use.

B) Patient has Already Received a Course of a Rituximab Product for Immunoglobulin G4-Related Disease (IgG4-RD). Approve for 1 month if the patient has had a positive response to a previous course of a rituximab product for immunoglobulin G4-related disease (IgG4-RD).

Dosing.[36-37] Approve ONE of the following (A or B):
A) Up to 375 mg/m^2 administered intravenously with doses separated by at least 7 days; OR
B) Up to two 1,000-mg doses administered as an intravenous infusion separated by at least 2 weeks.

22. Minimal Change Disease.[27]

Criteria.[27] Approve for the duration noted if the patient meets ONE of the following (A or B)
A) Initial Therapy. Approve for 1 month if the patient meets ONE of the following (i or ii):
- **i.** The patient meets ALL of the following (a, b, and c):
  - **a.** The patient is < 18 years of age; AND
  - **b.** The patient has steroid-dependent, steroid-sensitive nephrotic syndrome; AND
  - **c.** The patient meets one of the following (1 or 2):
    1. The patient has continuing frequent relapses despite optimal combinations of prednisone and corticosteroid-sparing agents; OR
    2. The patient has had serious adverse effects of therapy; OR
- **ii.** The patient meets ALL of the following (a, b and c):
  - **a.** The patient is ≥ 18 years of age; AND
  - **b.** The patient has frequently relapsing or glucocorticoid-dependent minimal change disease; AND
  - **c.** The patient has failed to attain a durable remission with cyclophosphamide or calcineurin inhibitors.

B) Patient has Already Received a Course of a Rituximab Product for Minimal Change Disease. Approve for 1 month if the patient has had a positive response to a previous course of a rituximab product for minimal change disease.

Dosing.[38] Approve ONE of the following (A or B):
A) Approve up to two 1,000-mg doses administered as an intravenous infusion separated by at least 2 weeks; OR
B) Approve up to 375 mg/m^2 administered intravenously with doses separated by at least 7 days.

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23. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).[27]

Criteria.[27] Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 1 month if the patient has failed intravenous immune globulin (IVIG), glucocorticoids, and plasma exchange.
B) Patient has Already Received a Course of a Rituximab Product for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). Approve for 1 month if the patient has had a positive response to a previous course of a rituximab product for chronic inflammatory demyelinating polyneuropathy (CIDP).

Dosing.[39] Approve up to 375 mg/m^2 administered intravenously with doses separated by at least 7 days.

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24. Sjogren's Syndrome.[27]

Criteria.[27] Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 1 month if the patient has tried corticosteroids and other immunosuppressive agents and these agents were ineffective.
B) Patient has Already Received a Course of a Rituximab Product for Sjogren's Syndrome. Approve for 1 month if the patient has had a positive response to a previous course of a rituximab product for Sjogren's syndrome.

Dosing.[40-41] Approve up to two 1,000-mg doses administered as an intravenous infusion separated by at least 2 weeks.

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25. Systemic Sclerosis.[27]

Criteria.[27] Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial Therapy. Approve for 1 month if the patient has tried corticosteroids and other immunosuppressive agents and these agents were ineffective.
B) Patient has Already Received a Course of a Rituximab Product for Systemic Sclerosis. Approve for 1 month if the patient has had a positive response to a previous course of a rituximab product for systemic sclerosis.

Dosing.[40-41] Approve up to two 1,000-mg doses administered as an intravenous infusion separated by at least 2 weeks.

Conditions Not Recommended for Approval.

Coverage of rituximab intravenous products is not recommended in the following situations:

1. Coverage is not recommended for circumstances *not* listed in the *Recommended Authorization Criteria*. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes	Date
Policy created	New Medicare Advantage Medical Policy	07/11/2018
Policy revision	Reviewed and revised original policy created 07/11/2018 in accordance with Local Coverage Article A52452 and Rituximab Intravenous Products Utilization Review Policy	08/28/2019
Policy revision	Completion of 2019 monthly monitoring process in accordance with Local Coverage Determination L33394, Local Coverage Article A52452, and Rituximab Intravenous Products Utilization Review Policy.	12/11/2019
Policy revision	Non-clinical update to policy to add the statement "This policy incorporates Medicare coverage guidance as set forth in National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs), as well as in companion policy articles and other guidance applicable to the relevant service areas. These documents are cited in the References section	1/30/2020

	of this policy. In some cases, this guidance includes specific lists of HCPCS and ICD-10 codes to help inform the coverage determination process. The Articles that include specific lists for billing and coding purposes will be included in the Reference section of this policy. However, to the extent that this policy cites such lists of HCPCS and ICD-10 codes, they should be used for reference purposes only. The presence of a specific HCPCS or ICD-10 code in a chart or companion article to an LCD is not by itself sufficient to approve coverage. Similarly, the absence of such a code does not necessarily mean that the applicable condition or diagnosis is excluded from coverage."	
Policy revision	*Multiple indications – changed "prescribing physician" to "prescriber" * **B-Cell Lymphoma:** Pediatric Aggressive Mature B-cell Lymphoma was added as an example of a B-cell lymphoma * **Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis:** For follow-up treatment of patients who have received induction treatment for ANCA-associated vasculitis, the maintenance dose was changed to be up to 1,000 mg per dose (previously was up to 500 mg). * **Acute Lymphoblastic Leukemia (ALL):** To align with updated NCCN guidelines, the requirement that patients who are Philadelphia-chromosome-positive try a tyrosine kinase inhibitor prior to rituximab was removed from the policy. * **Graft Versus Host Disease (GVHD):** To align with updated NCCN guidelines and other policies, criteria were changed to require at least one conventional systemic treatment prior to a rituximab product. Previously, criteria required that the patient had tried at least one other immunosuprressant or be concurrently receiveing an immunosuppressant in combination with rituximab	06/12/2020
Policy revision	**Riabni:** This newly approved biosimilar was added to the policy. There are no changes to the criteria, which apply to all rituximab products included in this policy.	01/12/2021
Policy revision	**Antineutrophil Cytoplasmic Antibody-Associated Vasculitis:** An alternative dosing regimen (up to 250 mg/m^2 for two doses, then up to 250 mg/m^2 not more frequently than once every 6 months) was added. **Acute Lymphoblastic Leukemia:** The Dosing was updated to require a minimum of 7 days between doses (previously was 14 days). **Hairy Cell Leukemia:** The requirement of relapsed or refractory disease was removed. **Primary Central Nervous System Lymphoma:** This condition of approval was added to the policy. **Systemic Lupus Erythematous (SLE) [Lupus]:** A note was added to clarify this includes nephrotic syndrome in a patient with SLE.	07/07/2021
Policy revision	**Antineutrophil Cytoplasmic Antibody-Associated Vasculitis:** The minimum amount of time required between doses was removed from the **Dosing** (not needed since addressed in clinical criteria). For initial therapy, up to two 1,000-mg intravenous doses separated by at least 2 weeks was added as an alternative induction dose. For follow-up treatment of a patient who has received induction treatment, the dosing was separated by age (≥ 18 or < 18 years of age); previously, dosing applied to all patients regardless of age. For a patient ≥ 18 years of age, the dose is up to 1,000 mg intravenously, whereas the dose is based on body surface area (250 mg/m^2) if < 18 years of age. Alternative induction doses were removed from the criteria (not needed).	7/21/2021
Policy revision	**B-Cell Lymphoma:** High-grade B-cell lymphoma was added as an example of a B-Cell Lymphoma. To align with guidelines, dosing was updated to approve up to two doses per cycle. **Rheumatoid Arthritis:** Note was clarified to state that a previous trial of a biologic applies to one biologic other than the requested drug. A biosimilar of the requested biologic does not count. A requirement was added for a patient who has already received two or more courses of a rituximab product to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber.	08/04/2022

	Graft-Versus-Host Disease: For initial therapy, the initial approval was changed to be for 1 month (previously was for 1 year). A requirement was added for a patient who has already received a course of a rituximab product to have at least one objective or subjective response to therapy. **Multiple Sclerosis:** For the required previous trial of at least one other disease-modifying agent for multiple sclerosis, it was clarified that inadequate efficacy or significant intolerance was according to the prescriber. Examples of disease-modifying agents used for multiple sclerosis were moved to an appendix (previously listed as examples in a note within the criteria). For a patient who has been receiving a rituximab product for 1 year or longer, response criteria were developed for reauthorization in which the patient either experienced a beneficial clinical response when assessed by at least one objective measure (with examples provided in a Note), or the patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation.	
Policy revision	**Removed the following indications:** Pre-transplant to suppress panel reactive anti-HLA antibodies in patients with high Panel Reactive Antibody (PRA) Levels to Human Leukocyte Antigens (HLA); Dermatomyositis or Polymyositis; and Grave's Disease/Ophthalmopathy. **Added the following indications:** Antibody-Mediated Rejection (AMR); Immune-Mediated Myopathy/Idiopathic Inflammatory Myopathy; Hemophilia (Acquired); Thrombotic Thrombocytopenic Purpura (Acquired); Immunoglobulin G4-Related Disease (IgG4-RD); Minimal Change Disease; Chronic Inflammatory Demyelinating Polyneuropathy (CIDP); Sjogren's Syndrome and Systemic Sclerosis.	03/01/2023
Policy revision	**Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis:** Dosing was updated to specify a total of four doses for initial therapy. For follow up treatment, a total of six doses was specified for patients $\geq$ 18 years of age and two doses for patients < 18 years of age. **Immunotherapy-Related Toxicities Associated with Checkpoint Inhibitors:** This condition of approval was added. **Neuromyelitis Optica Spectrum Disorder:** A total of four weekly doses for a regimen of 375 mg/m^2 intravenous was specified.	09/26/2023

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

Medication	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)
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)
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