PART B DRUG MEDICAL/PHARMACY	ASPIRE HEALTH	Effective Date January 1, 2024	
	RITUXIMAB PRODUCTS RITUXAN®, TRUXIMA®, RUXIENCE™, RIABNI™	Policy # Rituximab Products	
		Review Date 11/29/2023	**Applicable to:** ☑ Medicare Advantage ☐ Commercial ☐ Elevance Health HMO ☐ Blue Shield Trio
	Approver's Name & Title QI & UM Drug Subcommittee		

Aspire Health Plan applies medical drug clinical criteria as a reference for medical policy information only. Federal and state laws or requirements, contract language, and Plan benefit may take precedence over the application of these clinical criteria. Please consult the applicable certificate or contract for benefit details. This policy is subject to revision at the discretion of the Plan and is therefore subject to change. Refer to the disclaimer section below for more information.

Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals

POLICY

This policy addresses the coverage of rituximab products: Rituxan (rituximab); Riabni (rituximab-arrx); Ruxience (rituximab-pvvr); Truxima (rituximab-abbs) and Rituxan Hycela (rituximab/hyaluronidase).

NOTE: Any U.S. Food and Drug Administration approved and launched rituximab biosimilar product not listed by name in this policy will be considered non-preferred until reviewed by Aspire Health.

APPLICABLE HCPCS

J9312: Injection, rituximab, 10 mg; 1 billable unit = 10 mg (Rituxan IV only)
J9311: Injection, rituximab 10 mg and hyaluronidase (Rituxan Hycela): 1 billable unit = 10 mg
Q5115: Injection, rituximab-abbs, biosimilar, (Truxima), 10 mg; 1 billable unit = 10 mg
Q5119: Injection, rituximab-pvvr, biosimilar, (Ruxience), 10 mg; 1 billable unit = 10 mg
Q5123: Injection, rituximab-arrx, biosimilar, (Riabni), 10 mg; 1 billable unit = 10 mg

Available as:

- Rituximab and biosimilars: 100 mg/10 mL and 500 mg/50 mL (single-dose vials for IV injection)
- Rituxan Hycela 1,400 mg/23,400 Units per 11.7 mL single-dose vial:
- Rituxan Hycela 1,600 mg/26,800 Units per 13.4 mL single-dose vial:

Limitations of use: Rituxan Hycela (the subcutaneous Rituxan product)

- At least one full dose of a rituximab product by intravenous infusion must be administered before the subcutaneous Rituxan Hycela can be used.
- Rituximab/hyaluronidase (Rituxan Hycela) is not indicated for the treatment of non-malignant conditions, as is Rituximab and biosimilars.

CLINICAL CRITERIA

I. INITIAL CRITERIA

Rituximab may be authorized when **ALL** of the following criteria have been met with documentation (i.e., office chart notes, treatment response to previous therapy or drug regimens, lab results, treatment plan, other relevant clinical information).

A. The requested medication must be supported by **ONE** of the following:

1. An FDA-approved product labeling, **or**

2. A compendia-accepted indication in a CMS-approved compendia and listed with an appropriate level of evidence of efficacy:

    a. The National Comprehensive Cancer Network (NCCN): The level of evidence for the indication is Category 1 or 2A.

    NOTE: If a Prescriber chooses a NCCN level 2B in support of a chemotherapeutic drug used for an off-label indication, please submit peer-reviewed phase II or phase III studies demonstrating such support.

    b. DrugDex: The level of evidence for the indication is a Class I, Class IIa, or Class IIb.

    c. AHFS-DI or Clinical Pharmacology: The narrative text is supportive.

    d. Lexi-Drugs: The indication is listed as "Use: Off-Label" and rated as "Evidence Level A."

    e. National Comprehensive Cancer Network (NCCN) current recommendation of Category level 1 or 2A. Clinical Practice Guidelines and/or NCCN Drugs & Biologics Compendium. Refer to Appendix for Definition of Category 1 or 2A.

NOTE: The use must is not listed as unsupported, not indicated, not recommended (or equivalent terms) in any of the compendia. Any such listing does not meet authorization requirements.

**Refer to Appendix for Labeled and Compendia-accepted indications*.

AND

B. Dosing is in accordance with the FDA approved labeling; or
For compendia-accepted indications without FDA approved dosing, the dose prescribed is in accordance to CMS-approved compendia.

AND

C. Member has been evaluated/screened for the presence of the following conditions and meets **ALL** of the following:
    1. No active infection; and
    2. No untreated active or latent tuberculosis; and
    3. Hepatitis B surface antigen (HBsAg) negative; and
    4. No concurrent treatment with ANY of the following:
        i. Biological disease-modifying antirheumatic drugs (DMARDs), including any tumor necrosis factor (TNF) antagonists [Cimzia®, Enbrel®, Simponi®, Avsola™, Inflectra™, Remicade®, Renflexis™], interleukin agents [Arcalyst® (IL-1 blocker), Ilaris® (IL-1 blocker), Kineret® (IL-1RA), Actemra® (IL-6RA), Kevzara® (IL6RA), Stelara® (IL-12/23 inhibitor), Cosentyx® (IL-17A inhibitor), Taltz® (IL-17A inhibitor), Siliq™ (IL-17RA), Ilumya™ (IL-23 inhibitor), Skyrizi™ (IL-23 inhibitor), Tremfya® (IL-23 inhibitor)], janus kinase inhibitors (JAKi) [Xeljanz®/Xeljanz® XR, Rinvoq™], anti-

CD20 monoclonal antibodies [Rituxan®, Riabni™, Ruxience™, Truxima®, and Rituxan Hycela®], selective co-stimulation modulators [Orencia®], or integrin receptor antagonists [Entyvio®] because of the possibility of increased immunosuppression, neutropenia and increased risk of infection. List is not all-inclusive.

ii. Live vaccines.

and

5. Member is up-to-date with all immunizations in accordance with vaccination guidelines; and

6. For Rituxan Hycela requests only: Not prescribed for use with intravenous chemotherapy agents

II. REAUTHORIZATION / CONTINUATION OF THERAPY CRITERIA

Infliximab may be authorized for continuation of therapy when initial criteria have been met AND there is documentation of beneficial response from previous course of treatment:

A. Positive response to therapy: Stabilization or improvement in disease activity, signs and symptoms, or functional capacity as compared to baseline; **AND**

B. For Oncology Indications:

1. Tumor response with stabilization of disease or decrease in size of tumor or tumor spread; **and**

2. Member has not exceeded dosing or duration limits recommended by FDA labeling or CMS-approved compendia.

C. Absence of intolerance or adverse events from the previous course of treatment.

STEP THERAPY

Step therapy criteria do not apply for members who are currently being treated with the requested medications. Step therapy is only applied for members that are new to therapy (have not received the requested drug in the last 365 days.

NOTE: Step Therapy is not applicable to Rituxan Hycela (rituximab/hyaluronidase).

A. **PREFERRED PRODUCT(S): Ruxience (rituximab-pvvr)**

B. NON-PREFERRED PRODUCTS may be authorized when ALL of the clinical criteria above are met **AND ONE** of the following:

1. Information has been provided that indicates the patient has been treated with the request medication in the past 365 days; **OR**

2. Documentation that the member has had an ineffective treatment response to the active ingredient(s) of preferred medication(s); **OR**

3. Documented intolerance, hypersensitivity, or FDA labeled contraindication to the active ingredient(s) of preferred medication(s); **OR**

4. Clinical rationale from Prescriber indicating preferred medication(s) are likely to be ineffective, likely to cause an adverse reaction or harm, or likely to be of no clinical benefit; **OR**

5. For ONCOLOGY INDICATIONS

BOTH of the following must be met (a and b):

a. NCCN does NOT specify the preferred drug(s) as a "preferred" regimen for the requested indication (while excluding the requested drug from the "preferred" list); and

b. The requested medication is a Category I, high-level evidence with uniform consensus; or Category IIA for the requested indication.

DOSAGE AND AUTHORIZATION TIMEFRAMES

1. Recommended Dosage

a. The requested dose must be is within FDA-labeled dosing or supported in compendia for the requested indication [Riabni Prescribing Information; Rituxan Prescribing Information ; Rituxan Hycela Ruxience Prescribing Information: Truxima Prescribing Information].

b. For indications without FDA approved dosing, the requested dose is in accordance with CMS-compendia recommendations.

c. For Rituxan Hycela: All patients must receive at least ONE full dose of IV rituximab (without experiencing severe adverse reactions) prior to initiating treatment with subcutaneous rituximab/hyaluronidase; patients who do not tolerate a full IV dose should continue to receive IV rituximab in subsequent cycles. May switch to subcutaneous rituximab/hyaluronidase when a full IV dose is successfully administered.

2. Quantity

a. Quantity: Must be within the FDA-labeled dosing or supported in compendia for the requested indication and should not exceed single dose limit of rituximab products 500 mg/m² (CLL) and 375 mg/m^2 (NHL);

b. Waste Management for ALL Indications. Dosing is either a standard dose (e.g., 1,000 mg/dose) or the dose is based on body surface area (kg/m^2). If a standard dose is used, use the lowest amount of Rituxamab possible to achieve the dose required. If the dose is based on body surface area, the dose should be calculated, and the number of vials needed assessed.

3. Authorization Period

a. May be authorized for up to 12 months and reauthorized if member meets ALL of the 'Continuation of Therapy criteria or as otherwise specified in the CMS approved compendia.

b. Oncologic Indications: Maintenance therapy for oncology indications (excluding ALL) may be reauthorized for up to a maximum of 2 years.

NOTE: Rituximab products are used in defined treatment periods when used in oncologic indications. The package labeling recommends that rituximab be used up to 2 years where it is indicated as maintenance therapy. As treatment periods are definite, NCCN notes that the biosimilar may be substituted for the reference product at the initiation of a course of treatment. Additionally, no biosimilar rituximab agent is approved as interchangeable, so the patient should remain on the same product that was used to initiate treatment during a single course of therapy. There is currently inadequate evidence to support the efficacy and safety of switching between the reference and biosimilar products in the treatment of oncologic indications.

4. RITUXAN HYCELA (rituximab/hyaluronidase) ONLY:

   a. Authorize ONE full dose of the rituximab product (refer to Step Therapy) when criteria have been met for approved indications.

   b. Limitations of Use:
      i. Initiate treatment with Rituxan Hycela only after patients have received at least ONE full dose of a rituximab product by intravenous infusion; and
      ii. Rituximab/hyaluronidase is for subcutaneous administration only. Do not substitute rituximab (IV) for rituximab/hyaluronidase (subcutaneous). Use caution during product selection, preparation, and administration.
      iii. Rituxan Hycela is not indicated for the treatment of non-malignant conditions. Rituximab/hyaluronidase (for subcutaneous administration) and rituximab (for IV administration) are not interchangeable. Rituxan IV is indicated for treatment of RA. Rituxan Hycela has not been evaluated and does not have established dosing for RA.

DRUG INFORMATION

PHARMACOLOGIC CATEGORY: Antineoplastic Agent, Anti-CD20; Immunosuppresent Agent, Monoclonal Antibody

PRODUCTS: Rituxan (rituximab); Riabni (rituximab-arrx); Ruxience (rituximab-pvvr); Truxima (rituximab-abbs); Rituxan Hycela (rituximab/hyaluronidase)

ROUTE OF ADMINISTRATION: Intravenous Infusion

FDA-APPROVED INDICATIONS:

Rituxan and Rituximab Biosimilars (Ruxience, Truxima, and Riabni)

1. Chronic lymphocytic leukemia (CLL), in combination with fludarabine and cyclophosphamide (FC), fo the treatment of adult patients with previously untreated and previously treated CD20-positive CLL.
   Note: Other medications (e.g., idelalisib, venetoclax, ibrutinib) have approval for use in combination with rituximab for the treatment of relapsed or refractory CLL.
2. Granulomatosis with Polyangiitis (Wegener's granulomatosis) and Microscopic Polyangiitis, in combination with glucocorticoids: Treatment in adults (Rituxan and rituximab biosimilars); treatment in pediatric patients ≥2 years of age (Rituxan only).
3. Non-Hodgkin Lymphomas (NHL):
   Treatment of CD20-positive NHL in *adults* with:
   a. Relapsed or refractory, low-grade or follicular B-cell NHL (as a single agent).
   b. Follicular B-cell NHL, previously untreated (in combination with first-line chemotherapy, and as single-agent maintenance therapy in patients achieving a complete or partial response to rituximab with chemotherapy).
   c. Non-progressing (including stable disease), low-grade B-cell NHL (as a single agent after first-line cyclophosphamide, vincristine, and prednisone [CVP] treatment).
   d. Diffuse large B-cell NHL, previously untreated (in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP] chemotherapy or other anthracycline-based regimen).
   Treatment of CD20-positive NHLs in *pediatric patients ≥6 months* with:
   a. Previously untreated, advanced stage diffuse large B-cell lymphoma, Burkitt lymphoma, Burkitt-like lymphoma, or mature B-cell acute leukemia (in combination with chemotherapy).
5. Rheumatoid Arthritis (RA): RA in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies.

Rituxan Only

1. NHL: Treatment of CD20-positive NHLs in pediatric patients ≥ 6 months of age with previously untreated, advanced stage diffuse large B-cell lymphoma, Burkitt lymphoma, Burkitt-like lymphoma, or mature B-cell acute leukemia (in combination with chemotherapy).
2. Pemphigus vulgaris: Treatment of moderate to severe pemphigus vulgaris in adults.

COMPENDIAL APPROVED (OFF-LABELED) USES:

1. Acquired hemophilia
2. Autoimmune hemolytic anemia
3. B-cell lymphoma
4. Cardiac transplant rejection, Antibody-mediated, adjunctive treatment
5. Chronic lymphoid leukemia, In combination for first-line treatment
6. Chronic lymphoid leukemia, Maintenance, following rituximab-containing chemotherapy
7. Desensitization therapy - Transplantation of heart
8. Evans syndrome, Refractory to immunosuppressive therapy
9. Graft-versus-host disease, chronic, Steroid-refractory
10. Hodgkin's disease, CD20-positive, as monotherapy
11. Idiopathic inflammatory myopathy, Refractory
12. Immune thrombocytopenia
13. Immune thrombocytopenia, Previously treated
14. Liver transplant rejection, Antibody-mediated, adjunctive treatment
15. Lung disease with systemic sclerosis
16. Lung transplant rejection, Antibody-mediated
17. Lupus nephritis, Refractory
18. Mantle cell lymphoma, Maintenance, following first-line induction therapy
19. Mantle cell lymphoma, Untreated, induction therapy, in combination with anthracycline-based regimens
20. Minimal change disease, Refractory, steroid-dependent or steroid-resistant
21. Myasthenia gravis, Refractory
22. Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia, CD20-positive, in combination with chemotherapy
23. Post-transplant lymphoproliferative disorder
24. Primary Sjögren's syndrome
25. Rejection of intestine transplant; Prophylaxis
26. Relapsing remitting multiple sclerosis
27. Rheumatoid arthritis, In combination with methotrexate, in patients with an inadequate response to methotrexate
28. Systemic lupus erythematosus, Refractory to immunosuppressive therapy
29. Thrombotic thrombocytopenic purpura, In combination with steroids and plasma exchange
30. Thyroid eye disease (Moderate to Severe), Second line therapy, excluding patients with risk for dysthyroid optic neuropathy
31. Waldenstrom macroglobulinemia

NOTE: *Off-Label / Investigational Uses*

Other off-label uses that meet coverage criteria will be considered for coverage at the discretion of Aspire Health. Requests for indications other than those listed in this policy must be submitted with relevant supporting evidence from CMS approved compendia.

BOXED WARNINGS

1. Fatal Infusion-related Reactions: Severe, sometimes fatal infusion-related effects reported. Death has occurred within 24 hours of administration. Approximately 80% of fatal reactions have occurred with the first dose. Monitor patients carefully during infusions. If grade 3 or 4 infusion reactions occur, discontinue rituximab infusion and institute appropriate treatment.
2. Severe Mucocutaneous Reactions: Risk of severe, sometimes fatal, mucocutaneous reactions.

3. HBV Reactivation: Reactivation of HBV infection (including fulminant hepatitis and hepatic failure), sometimes fatal, reported. Screen all patients for HBV infection prior to initiation of therapy. Discontinue rituximab and concomitant chemotherapy if HBV reactivation occurs.
4. Progressive Multifocal Leukoencephalopathy (PML): Risk of potentially fatal PML, secondary to JC virus infection.

CONTRAINDICATIONS:
There are no contraindications listed in the manufacturer's labeling.

CLINICAL SUMMARY / APPENDIX

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

NCCN Categories of Evidence and Consensus
The specific definitions of the NCCN categories for recommendations are included below:

- Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate;
- Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate;
- Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate;
- Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Rituxan Hycela (rituximab/hyaluronidase human) is a combination of rituximab and hyaluronidase human and contains the identical molecular antibody of rituximab available in Rituxan IV, but hyaluronidase has been added to facilitate systemic delivery as it increases the absorption rate of rituximab-containing products by increasing permeability of subcutaneous tissue through temporary depolymerization of hyaluronan. At the recommended doses, hyaluronidase acts locally, and the effects are reversible. The permeability of the subcutaneous tissue is restored within 24 to 48 hours. Rituxan Hycela should be administered under the care of a healthcare professional with appropriate medical support to manage severe and potentially fatal reactions. The dose of Rituxan Hycela is fixed regardless of the patient's body surface area; dose reductions are not recommended. When given in combination with chemotherapy, reduce the dose of chemotherapeutic drugs to manage adverse events. Rituxan Hycela is not indicated for the treatment of non-malignant conditions.

REFERENCES

Government Agency

1. Centers for Medicare and Medicaid Services (CMS). Medicare coverage database: National coverage determination (NCD) (search: Rituximab: Riabni, Rituxan, Ruxience, Truxima). Available from CMS. No NCD identified (LCD available but not applicable to MAC).
2. CMS IOM, Publication 100-02, Medicare Benefit Policy Manual, Chapter 15, Section 50.4.5
3. CMS Transmittal 96, Change Request (CR) 6191 .

Prescribing Information

1. Riabni (rituximab) [prescribing information]. Thousand Oaks, CA: Amgen Inc; June 2022.
2. Rituxan (rituximab) [prescribing information]. South San Francisco, CA: Genentech Inc; December 2021.
3. Rituxan Hycela (rituximab/hyaluronidase human) [prescribing information]. South San Francisco, CA: Genentech Inc; June 2021.

4. Truxima (rituximab-abbs) [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA Inc; April 2023.

Peer Reviewed Literature, Guidelines

1. Milliman Care Guidelines (MCG). Ambulatory Care 27th Edition ACG: A-0448 (AC). 2023.
2. Farez MF, Correale J, Armstrong MJ, et al. Practice guideline update summary: vaccine-preventable infections and immunization in multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2019;93(13):584-594. doi:10.1212/WNL.0000000000008157.
3. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res. 2016;68(1):1-25.

IMPORTANT REMINDER

This Medicare Part B Step Therapy Medical Necessity Guideline is provided for informational purposes only and neither constitutes nor replaces professional medical advice. Physicians, hospitals, and other providers are expected to administer or use drugs/biologicals in the most effective and clinically appropriate manner. Treating physicians and other health care providers are solely responsible for all medical care decisions. In accordance with the member's Evidence of Coverage (EOC), every benefit plan has its own coverage provisions, limitations, and exclusions. In the event of a conflict between this policy and the member's EOC, the member's EOC provisions will take precedence.

Aspire Health Plan (AHP) adheres to Medicare guidelines, including National Coverage Determination (NCD), Local Coverage Determinations (LCDs), Local Coverage Articles (LCAs), and other relevant Medicare manuals established by CMS. Compliance with these guidelines is required when applicable. Refer to the CMS website at http://www.cms.hhs.gov. For the most up-to-date Medicare policies and coverage, please search the Medicare Coverage Database. All LCDS are the same for each state within a Jurisdiction. Medicare Part B Administrative Contractor (MAC) for CA [Jurisdiction E (1)]: Active LCDs - JE Part B – Noridian (noridianmedicare.com). In the event of a discrepancy between this policy and the Medicare NCD or LCD, the Medicare NCD/LCD will govern.

This policy is utilized by AHP to determine coverage in the absence of applicable CMS Medicare guidelines. Please refer to the links provided in the References section below to access the Medicare source materials that were used for developing this resource document. This document does not serve as a substitute for the official Medicare source materials that provide detailed information on Medicare coverage requirements. In the event of a conflict between this document and Medicare source materials, the Medicare source materials will take precedence.

The inclusion of a code in this policy does not imply that the health service it describes is covered or not covered. Benefit coverage for health services is determined by the member-specific plan document and applicable laws that may mandate coverage for a particular service. Inclusion of a code does not imply or guarantee reimbursement or payment of a claim. Other Policies and Standards may also apply. Providers are expected to retain or have access to the necessary documentation when requested in order to support coverage.

POLICY HISTORY

Version	Date	Revision Author/Title	Summary of Changes
1	11/29/2023		New Policy