

Clinical Policy: Rituximab (Rituxan), Rituximab-arrx (Riabni), Rituximab-pvvr (Ruxience), Rituximab-abbs (Truxima), Rituximab-Hyaluronidase (Rituxan Hycela)

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[Coding Implications](#)
[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

Rituximab (Rituxan[®]) is a human monoclonal immunoglobulin G-1 (IgG1) kappa antibody directed against the CD20 antigen.

Rituximab-arrx (Riabni[™]) is a CD20-directed cytolytic antibody and biosimilar to Rituxan for the listed Riabni indications.

Rituximab-pvvr (Ruxience[™]) is a CD20-directed cytolytic antibody and biosimilar to Rituxan for the listed Ruxience indications.

Rituximab-abbs (Truxima[®]) is a CD20-directed cytolytic antibody and biosimilar to Rituxan for the listed Truxima indications.

Rituximab and hyaluronidase (Rituxan Hycela[™]) is a combination of rituximab and human hyaluronidase that is used to increase the dispersion and absorption of the co-administered drugs when given subcutaneously.

FDA Approved Indication(s)

Indications		Rituxan	Riabni	Ruxience	Truxima	Rituxan Hycela*
<i>Oncology indications (adults)</i>						
Low-grade and follicular B-cell NHL	Relapsed or refractory, low-grade [Rituxan, Riabni, Ruxience, Truxima] or follicular [Rituxan, Riabni, Ruxience, Truxima, Rituxan Hycela], CD20-positive, B-cell NHL as a single agent	X	X	X	X	X
	Previously untreated follicular, CD20-positive B-cell NHL in combination with first-line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy	X	X	X	X	X

CLINICAL POLICY

Rituximab, Rituximab-arrx, Rituximab-pvvr, Rituximab-abbs,
Rituximab-Hyaluronidase



Indications		Rituxan	Riabni	Ruxience	Truxima	Rituxan Hycela*
	Non-progressing (including stable disease), low-grade [<i>Rituxan, Riabni, Ruxience, Truxima</i>] or follicular [<i>Rituxan Hycela</i>], CD20-positive B-cell NHL as a single agent after first-line CVP chemotherapy	X	X	X	X	X
DLBCL (a B-cell NHL)	Previously untreated CD20-positive DLBCL in combination with CHOP or other anthracycline-based chemotherapy regimens	X	X	X	X	X
CLL (a B-cell NHL)	Previously untreated and treated CD20-positive CLL in combination with FC chemotherapy	X	X	X	X	X
<i>Non-oncology indications (adults)</i>						
RA	Moderately to severely active RA in combination with MTX in patients who have inadequate response to one or more TNF antagonist therapies	X			X	
GPA, MPA	GPA and MPA in combination with glucocorticoids	X	X	X	X	
PV	Moderate to severe PV	X				

Abbreviations: CLL (chronic lymphocytic leukemia), DLBCL (diffuse large B-cell lymphoma), GPA (granulomatosis with polyangiitis; Wegener's granulomatosis), MPA (microscopic polyangiitis), NHL (Non-Hodgkin's lymphoma), PV (pemphigus vulgaris), RA (rheumatoid arthritis).

**Rituxan Hycela limitations of use: 1) Initiate treatment with Rituxan Hycela only after patients have received at least one full dose of a rituximab product by intravenous infusion; 2) Rituxan Hycela is not indicated for the treatment of non-malignant conditions.*

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Rituxan, Ruxience, Truxima, and Rituxan Hycela are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Non-Hodgkin's Lymphoma (includes CLL) (must meet all):

1. Diagnosis of any of the following non-Hodgkin's lymphoma (NHL) subtypes (a-m):
 - a. AIDS-related B-cell lymphomas;
 - b. Burkitt lymphoma;
 - c. Castleman's disease;
 - d. Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)

- e. Diffuse large B-cell lymphoma (DLBCL);
 - f. Follicular lymphoma (FL);
 - g. Hairy cell leukemia (Rituxan/Riabni/Ruxience/Truxima only);
 - h. Low- or high-grade B-cell lymphoma;
 - i. MALT lymphoma (gastric or nongastric);
 - j. Mantle cell lymphoma;
 - k. Marginal zone lymphoma (nodal or splenic);
 - l. Post-transplant lymphoproliferative disorder;
 - m. Primary cutaneous B-cell lymphoma;
2. Prescribed by or in consultation with an oncologist or hematologist;
 3. Member meets one of the following (a or b):
 - a. Age \geq 18 years;
 - b. Age $<$ 18 years with aggressive mature B-cell lymphoma;
 4. If request is for Rituxan, Riabni, or Truxima, member meets one of the following (a or b):
 - a. Member must use Ruxience, unless contraindicated or clinically significant adverse effects are experienced;
**Prior authorization may be required for Ruxience*
 - b. Request is for Stage IV or metastatic cancer for a State with regulations against step therapy in advanced oncology settings (*see Appendix E*);
 5. If request is for Rituxan Hycela, member has received at least one full dose of Rituxan, Riabni, Ruxience, or Truxima;
 6. Request meets either of the following (a or b):*
 - a. Dose does not exceed (i or ii):
 - i. Rituxan/Riabni/Ruxience/Truxima: 500 mg/m² per IV infusion (*see Section V for cycle regimens*);
 - ii. Rituxan Hycela: 1,600 mg/26,800 units per SC injection (*see Section V for cycle regimens*);
 - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).
**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months**B. Rheumatoid Arthritis (must meet all):**

1. Diagnosis of RA per American College of Rheumatology (ACR) criteria (*see Appendix F*);
2. Request is for Rituxan/Riabni/Ruxience/Truxima;
3. Prescribed by or in consultation with a rheumatologist;
4. Age \geq 18 years;
5. Member meets one of the following (a or b):
 - a. Failure of a \geq 3 consecutive month trial of MTX at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
 - b. If intolerance or contraindication to MTX (*see Appendix D*), failure of a \geq 3 consecutive month trial of at least ONE conventional disease-modifying

- antirheumatic drug [DMARD] (e.g., sulfasalazine, leflunomide, hydroxychloroquine) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
6. Failure of Inflectra or Renflexis, unless contraindicated or clinically significant adverse effects are experienced;
**Prior authorization may be required for Inflectra and Renflexis*
 7. Documentation of one of the following baseline assessment scores (a or b):
 - a. Clinical disease activity index (CDAI) score (*see Appendix G*);
 - b. Routine assessment of patient index data 3 (RAPID3) score (*see Appendix H*);
 8. If request is for Rituxan, Riabni, or Truxima, member must use Ruxience (*see Appendix D*), unless contraindicated or clinically significant adverse effects are experienced;
**Prior authorization may be required for Ruxience*
 9. Rituxan/Riabni/Ruxience/Truxima will be administered in combination with MTX unless contraindicated or clinically significant adverse effects are experienced;
 10. Dose does not exceed two-1,000 mg IV infusions separated by 2 weeks followed by two-1,000 mg IV infusions every 16 weeks.

Approval duration: 6 months

C. Granulomatosis with Polyangiitis (Wegener's Granulomatosis) and Microscopic Polyangiitis (must meet all):

1. Diagnosis of GPA or MPA;
2. Request is for Rituxan/Riabni/Ruxience/Truxima;
3. Prescribed by or in consultation with a rheumatologist;
4. For Rituxan: age ≥ 2 years;
5. For age ≥ 18 years: If request is for Rituxan, Riabni, or Truxima, member must use Ruxience, unless contraindicated or clinically significant adverse effects are experienced;
**Prior authorization may be required for Ruxience*
6. Prescribed in combination with a glucocorticoid (e.g. prednisone, prednisolone, dexamethasone);
7. Dose does not exceed (a or b):
 - a. Induction: 375 mg/m² weekly for 4 weeks;
 - b. Follow up treatment: two-500 mg infusions separated by 2 weeks, then 500 mg every 6 months.

Approval duration: 6 months

D. Pemphigus Vulgaris and Pemphigus Foliaceus (must meet all):

1. Diagnosis of PV or pemphigus foliaceus (PF);
2. Request is for Rituxan/Riabni/Ruxience/Truxima;
3. Prescribed by or in consultation with a dermatologist;
4. Age ≥ 18 years;
5. If request is for Rituxan, Riabni, or Truxima, member must use Ruxience, unless contraindicated or clinically significant adverse effects are experienced;
**Prior authorization may be required for Ruxience*
6. Dose does not exceed (a or b):

- a. Initial: two-1,000 mg infusions separated by 2 weeks;
- b. Maintenance: 500 mg every 6 months (starting 12 months after initial dose).

Approval duration: 6 months

E. NCCN Compendium Indications (off-label) (must meet all):

1. Diagnosis of any of the following (a-g):
 - a. Acute lymphoblastic leukemia in patients who are CD20-positive;
 - b. Immune checkpoint inhibitor-related toxicities;
 - c. Graft-versus-host disease;
 - d. Leptomeningeal metastases from lymphoma;
 - e. Nodular lymphocyte-predominant Hodgkin lymphoma;
 - f. Primary CNS lymphoma;
 - g. Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma;
2. Request is for Rituxan/Riabni/Ruxience/Truxima;
3. Prescribed by or in consultation with an oncologist or hematologist;
4. Age \geq 18 years;
5. If request is for Rituxan, Riabni, or Truxima, member meets one of the following (a or b):
 - a. Member must use Ruxience, unless contraindicated or clinically significant adverse effects are experienced;
**Prior authorization may be required for Ruxience*
 - b. Request is for Stage IV or metastatic cancer for a State with regulations against step therapy in advanced oncology settings (*see Appendix E*);
6. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

F. Neuromyelitis Optica Spectrum Disorder (off-label) (must meet all):

1. Diagnosis of neuromyelitis optica spectrum disorder (NMOSD);
2. Request is for Rituxan/Riabni/Ruxience/Truxima;
3. Prescribed by or in consultation with a neurologist;
4. Age \geq 18 years;
5. Member has experienced at least one relapse within the previous 12 months;
6. Baseline Expanded Disability Status Scale (EDSS) score \leq 8;
7. If request is for Rituxan, Riabni, or Truxima, member must use Ruxience, unless contraindicated or clinically significant adverse effects are experienced;
**Prior authorization may be required for Ruxience*
8. Rituxan/Riabni/Ruxience/Truxima is not prescribed concurrently with Soliris[®], Enspryng[™], or Uplizna[®];
9. Request meets one of the following (a, b, or c):
 - a. Dose does not exceed 375 mg/m² per week for 4 weeks as induction, followed by 375 mg/m² biweekly every 6 to 12 months;
 - b. Dose does not exceed 1,000 mg biweekly every 6 to 12 months;

- c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months**G. Immune Thrombocytopenia (off-label) (must meet all):**

1. Diagnosis of immune thrombocytopenia (ITP);
2. Request is for Rituxan/Riabni/Ruxience/Truxima;
3. Prescribed by or in consultation with a hematologist;
4. Current (within 30 days) platelet count is < 30,000/ μ L or member has an active bleed;
5. Member meets one of the following (a or b):
 - a. Failure of a systemic corticosteroid;
 - b. Member has intolerance or contraindication to systemic corticosteroids, and failure of an immune globulin, unless contraindicated or clinically significant adverse effects are experienced (*see Appendix B*);
**Prior authorization may be required for immune globulins*
6. If request is for Rituxan, Riabni, or Truxima, member must use Ruxience, unless contraindicated or clinically significant adverse effects are experienced;
**Prior authorization may be required for Ruxience*
7. Rituxan/Riabni/Ruxience/Truxima is not prescribed concurrently with a thrombopoietin receptor agonist (e.g., Nplate[®], Promacta[®], Doptelet[®]);
8. Request meets one of the following (a, b, or c):
 - a. Dose does not exceed 375 mg/m² per week for 4 weeks;
 - b. Dose does not exceed 1,000 mg on days 1 and 15;
 - c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 1 month**H. Other diagnoses/indications**

1. Members with any of the following diagnoses may be covered if the off-label criteria policy is met:
 - a. Myasthenia gravis;
 - b. Nephrotic syndrome;
2. If request is for Rituxan, Riabni, or Truxima, member meets one of the following (a or b):
 - a. Member must use Ruxience, unless contraindicated or clinically significant adverse effects are experienced;
**Prior authorization may be required for Ruxience*
 - b. Request is for Stage IV or metastatic cancer for a State with regulations against step therapy in advanced oncology settings (*see Appendix E*);
3. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid.

II. Continued Approval**A. Immune Thrombocytopenia (off-label):**

1. Re-authorization is not permitted. Members must meet the initial approval criteria.

Approval duration: Not applicable

B. All Other Indications in Section I (must meet all):

1. Member meets one of the following (a or b):
 - a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
 - b. Documentation supports that member is currently receiving Rituxan, Riabni, Ruxience, Truxima, or Rituxan Hycela for a covered oncology indication and has received this medication for at least 30 days;
2. Meets one of the following (a, b, c, or d):
 - a. For NMOSD: Member is responding positively to therapy – including but not limited to improvement or stabilization in any of the following parameters:
 - i. Frequency of relapses;
 - ii. EDSS score;
 - iii. Visual acuity;
 - b. For PV or PF: Member is responding positively to therapy, or member has experienced relapse;
 - c. For RA: member is responding positively to therapy as evidenced by one of the following (i or ii):
 - i. A decrease in CDAI (*see Appendix G*) or RAPID3 (*see Appendix H*) score from baseline;
 - ii. Medical justification stating inability to conduct CDAI re-assessment, and submission of RAPID3 score associated with disease severity that is similar to initial CDAI assessment or improved;
 - d. For all other indications: Member is responding positively to therapy;
3. If request is for Rituxan, Riabni, or Truxima, member meets one of the following (a or b):
 - a. Member must use Ruxience, unless contraindicated or clinically significant adverse effects are experienced;
**Prior authorization may be required for Ruxience*
 - b. Request is for Stage IV or metastatic cancer for a State with regulations against step therapy in advanced oncology settings (*see Appendix E*);
4. For NMOSD: Rituxan/Riabni/Ruxience/Truxima is not prescribed concurrently with Soliris, Enspryng, or Uplizna;
5. If request is for a dose increase, request meets either of the following (a or b):*
 - a. New dose does not exceed the following:
 - i. NHL:
 - a) Rituxan/Riabni/Ruxience/Truxima: 500 mg/m² per IV infusion;
 - b) Rituxan Hycela: 1,600 mg/26,800 units per SC injection;
 - ii. RA (Rituxan/Riabni/Ruxience/Truxima): two-1,000 mg IV infusions every 16 weeks;
 - iii. GPA/MPA (Rituxan/Riabni/Ruxience/Truxima):
 - a) Induction: 375 mg/m² IV weekly for up to 4 weeks total;

- b) Follow-up treatment: two-500 mg IV infusions separated by two weeks, then 500 mg IV every 6 months;
- iv. PV or PF (Rituxan/Riabni/Ruxience/Truxima) (a or b):
 - a) Maintenance: 500 mg IV every 6 months (starting 12 months after initial dose);
 - b) Relapse: 1,000 mg IV once then 500 mg IV 16 weeks later, then 500 mg IV every 6 months;
- v. NMOSD (Rituxan/Riabni/Ruxience/Truxima): 375 mg/m² or 1,000 mg biweekly every 6 to 12 months;
- b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2):

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
Approval duration: Duration of request or 6 months (whichever is less); or
2. Members with any of the following diagnoses may be covered if the off-label criteria policy is met:
 - a. Myasthenia gravis;
 - b. Nephrotic syndrome;
3. If request is for Rituxan, Riabni, or Truxima, member meets one of the following (a or b):
 - a. Member must use Ruxience, unless contraindicated or clinically significant adverse effects are experienced;
**Prior authorization may be required for Ruxience*
 - b. Request is for Stage IV or metastatic cancer for a State with regulations against step therapy in advanced oncology settings (*see Appendix E*);
4. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

- A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents;
- B. Combination use of biological disease-modifying antirheumatic drugs (bDMARDs), 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[®] (IL-6RA), 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.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

- AAN: American Academy of Neurology
- ARR: annualized relapse rate
- CDAI: clinical disease activity index
- CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone
- CLL: chronic lymphocytic leukemia
- CVP: cyclophosphamide, vincristine, prednisone
- DLBCL: diffuse large B-cell lymphoma
- DMARD: disease-modifying antirheumatic drug
- EDSS: Expanded Disability Status Scale
- FC: fludarabine and cyclophosphamide
- FDA: Food and Drug Administration
- FL: follicular lymphoma
- GPA: granulomatosis with polyangiitis (Wegener’s granulomatosis)
- ITP: immune thrombocytopenia
- MALT: mucosa-associated lymphoid tissue
- MPA: microscopic polyangiitis
- MS: multiple sclerosis
- MTX: methotrexate
- NCCN: National Comprehensive Cancer Network
- NHL: Non-Hodgkin’s lymphoma
- NMOSD: neuromyelitis optica spectrum disorder
- PF: pemphigus foliaceus
- PPMS: primary progressive MS
- PV: pemphigus vulgaris
- RA: rheumatoid arthritis
- RAPID3: routine assessment of patient index data 3
- RCT: randomized controlled trial
- RRMS: relapsing-remitting MS
- SLL: small lymphocytic lymphoma

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
RA		
azathioprine (Azasan®, Imuran®)	1 mg/kg/day PO QD or divided BID	2.5 mg/kg/day
Cuprimine® (d-penicillamine) <i>Off-label</i>	<u>Initial dose:</u> 125 or 250 mg PO QD <u>Maintenance dose:</u> 500 – 750 mg/day PO QD	1,500 mg/day
cyclosporine (Sandimmune®, Neoral®)	2.5 – 4 mg/kg/day PO divided BID	4 mg/kg/day
hydroxychloroquine (Plaquenil®) <i>Off-label</i>	<u>Initial dose:</u> 400 – 600 mg/day PO QD <u>Maintenance dose:</u> 200 – 400 mg/day PO QD	5 mg/kg/day
leflunomide (Arava®)	100 mg PO QD for 3 days, then 20 mg PO QD	20 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
methotrexate (Rheumatrex [®])	7.5 mg/week PO, SC, or IM or 2.5 mg PO Q12 hr for 3 doses/week	30 mg/week
Ridaura [®] (auranofin)	6 mg PO QD or 3 mg PO BID	9 mg/day
sulfasalazine (Azulfidine [®])	2 g/day PO in divided doses	3 gm/day
Enbrel (etanercept)	25 mg SC twice weekly or 50 mg SC once weekly	50 mg/week
Humira (adalimumab)	40 mg SC every other week (may increase to once weekly)	40 mg/week
GPA, MPA		
glucocorticoids	Varies	Varies
ITP		
corticosteroids	Varies	Varies
immune globulins (e.g., Carimune [®] NF, Flebogamma [®] DIF 10%, Gammagard [®] S/D, Gammaked [™] , Gamunex [®] - C, Gammaplex [®] , Octagam [®] 10%, Privigen [®])	Refer to prescribing information	Refer to prescribing information

Therapeutic alternatives are listed as Brand name[®] (generic) when the drug is available by brand name only and generic (Brand name[®]) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): none reported
- Boxed warning(s):
 - Fatal infusion reactions (Rituxan, Riabni, Ruxience, Truxima)
 - Severe mucocutaneous reactions, hepatitis B virus reactivation, progressive multifocal leukoencephalopathy (Rituxan, Riabni, Ruxience, Truxima, Rituxan Hycela).

Appendix D: General Information

- Definition of MTX or disease-modifying antirheumatic drug (DMARD) failure
 - Child-bearing age is not considered a contraindication for use of MTX. Each drug has risks in pregnancy. An educated patient and family planning would allow use of MTX in patients who have no intention of immediate pregnancy.
 - Social use of alcohol is not considered a contraindication for use of MTX. MTX may only be contraindicated if patients choose to drink over 14 units of alcohol per week. However, excessive alcohol drinking can lead to worsening of the condition, so patients who are serious about clinical response to therapy should refrain from excessive alcohol consumption.
- Examples of positive response to RA therapy may include, but are not limited to:

- Reduction in joint pain/swelling/tenderness
- Improvement in ESR/CRP levels
- Improvements in activities of daily living
- Off-label use in multiple sclerosis (MS):
 - The off-label use of rituximab in relapsing-remitting MS (RRMS) and primary progressive MS (PPMS) is supported by Class IIB recommendations in Micromedex with the following clinical evidence:
 - RRMS: 1 randomized controlled trial (RCT) (N = 104) found there was a significant difference in T1-weighted lesion count at 24 weeks and annualized relapse rate (ARR) at 24 weeks (but not at 48 weeks) for patients receiving rituximab compared to placebo. Important limitations of this study are poor methodological quality and high risk of attrition bias resulting from a high dropout rate (40% in placebo and 15.9% in rituximab).
 - PPMS: 1 RCT (N = 439) found there was no significant difference in confirmed disability progression for patients receiving rituximab compared to placebo.
 - In the 2018 MS guidelines, the American Academy of Neurology (AAN) does not prefer any one disease-modifying therapy over another for the treatment of RRMS, except for Gilenya[®], Tysabri[®], and Lemtrada[®] for highly active disease. The recommended agent in PPMS is Ocrevus[®]. AAN makes the following comments on rituximab:
 - RRMS:
 - Rituximab is probably more effective than placebo in decreasing the risk of relapse at 1 year.
 - There is insufficient evidence to determine the efficacy of rituximab compared with placebo in decreasing the ARR at 1 year.
 - Rituximab is probably more effective than placebo in decreasing the volume of T2 lesions from baseline to week 36.
 - PPMS: The randomized controlled trial of rituximab in PPMS was promising but inconclusive.
- Off-label use in NMOSD:
 - Rituxan is considered a standard first-line treatments for NMOSD per clinical reviews and the 2010 European Federation of Neurological Societies guideline. Comparative analyses shows that rituximab significantly reduces attack frequency and stabilizes or reduces neurological disabilities while achieving long-term safety. Neurological disability was assessed via the EDSS score, which ranges from 0 (no disability) to 10 (death).
 - In a 5-year follow-up of 30 patients from a 2-year retrospective case series, 18 (60%) were relapse free and 28 (93%) had improved or stabilized disability as evidenced by improvement in the EDSS score. The mean (SD) pretreatment versus posttreatment annualized relapse rate (ARR) was 2.4 (1.5) versus 0.3 (1.0) ($p < 0.001$). No serious adverse events resulted in discontinuation of therapy.
 - In a 1-year RCT with 68 patients who had a baseline EDSS score ≤ 7 , rituximab demonstrated a higher proportion decrease in ARR (SD) than azathioprine (0.83 (0.37) compared to 0.56 (0.50), $p = 0.022$). The mean change in EDSS score (SD)

was -0.98 (1.14) with rituximab versus -0.44 (0.54) with azathioprine ($p < 0.001$). There were no statistically significant difference in adverse effects.

- A 2019 meta-analysis that included 26 studies and 577 patients showed a significant mean decrease in the ARR after rituximab therapy (-1.56 (95% CI -1.82 to -1.29)). There was no significant correlation found between AQP4-IgG serostatus and ARR or EDSS.
- Off-label use of Ruxience for RA:
 - While Ruxience currently does not have an FDA indication for RA, the biosimilar was studied in a phase 1 trial comparing its pharmacokinetics (PK) versus EU- and US-licensed reference rituximab, MabThera and Rituxan, respectively, in 220 patients with active RA.¹ The PK profiles of all 3 rituximab products were similar, and all resulted in sustained, profound B cell suppression up to week 25. The incidence of antidrug antibodies was similar across all 3 study arms, and no clinically meaningful differences in adverse events was noted.

Appendix E: States with Regulations against Redirections in Stage IV or Metastatic Cancer

State	Step Therapy Prohibited?	Notes
FL	Yes	For stage 4 metastatic cancer and associated conditions.
GA	Yes	For stage 4 metastatic cancer. Redirection does not refer to review of medical necessity or clinical appropriateness.
IA	Yes	For standard of care stage 4 cancer drug use, supported by peer-reviewed, evidence-based literature, and approved by FDA.
LA	Yes	For stage 4 advanced, metastatic cancer or associated conditions. Exception if “clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy.
OH	Yes	<i>*Applies to HIM requests only*</i> For stage 4 metastatic cancer and associated conditions
PA	Yes	For stage 4 advanced, metastatic cancer
TN	Yes	For advanced metastatic cancer and associated conditions
TX	Yes	For stage 4 advanced, metastatic cancer and associated conditions

Appendix F: The 2010 ACR Classification Criteria for RA

Add score of categories A through D; a score of ≥ 6 out of 10 is needed for classification of a patient as having definite RA.

A	Joint involvement	Score
	1 large joint	0
	2-10 large joints	1
	1-3 small joints (with or without involvement of large joints)	2
	4-10 small joints (with or without involvement of large joints)	3
	> 10 joints (at least one small joint)	5

B	Serology (at least one test result is needed for classification)	
	Negative rheumatoid factor (RF) <i>and</i> negative anti-citrullinated protein antibody (ACPA)	0
	Low positive RF <i>or</i> low positive ACPA <i>* Low: < 3 x upper limit of normal</i>	2
	High positive RF <i>or</i> high positive ACPA <i>* High: ≥ 3 x upper limit of normal</i>	3
C	Acute phase reactants (at least one test result is needed for classification)	
	Normal C-reactive protein (CRP) and normal erythrocyte sedimentation rate (ESR)	0
	Abnormal CRP or abnormal ESR	1
D	Duration of symptoms	
	< 6 weeks	0
	≥ 6 weeks	1

Appendix G: Clinical Disease Activity Index (CDAI) Score

The Clinical Disease Activity Index (CDAI) is a composite index for assessing disease activity in RA. CDAI is based on the simple summation of the count of swollen/tender joint count of 28 joints along with patient and physician global assessment on VAS (0–10 cm) Scale for estimating disease activity. The CDAI score ranges from 0 to 76.

CDAI Score	Disease state interpretation
≤ 2.8	Remission
> 2.8 to ≤ 10	Low disease activity
> 10 to ≤ 22	Moderate disease activity
> 22	High disease activity

Appendix H: Routine Assessment of Patient Index Data 3 (RAPID3) Score

The Routine Assessment of Patient Index Data 3 (RAPID3) is a pooled index of the three patient-reported ACR core data set measures: function, pain, and patient global estimate of status. Each of the individual measures is scored 0 – 10, and the maximum achievable score is 30.

RAPID3 Score	Disease state interpretation
≤ 3	Remission
3.1 to 6	Low disease activity
6.1 to 12	Moderate disease activity
> 12	High disease activity

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Rituxan and rituximab biosimilars	Low-grade and follicular B-cell NHL	<p>375 mg/m² IV infusion according to the following schedules:</p> <ul style="list-style-type: none"> • Relapsed or refractory, low-grade or follicular, CD20+, B-cell NHL <ul style="list-style-type: none"> ○ Once weekly for 4 or 8 doses ○ Retreatment: once weekly for 4 doses • Previously untreated, follicular, CD20+, B-cell NHL: <ul style="list-style-type: none"> ○ Administer on Day 1 of each cycle of chemotherapy for up to 8 doses; ○ If complete or partial response, initiate Rituxan/Truxima maintenance treatment as a single-agent every 8 weeks for 12 doses to start 8 weeks following completion of a rituximab product in combination with chemotherapy. • Non-progressing, low-grade, CD20+, B-cell NHL, after first-line CVP chemotherapy: <ul style="list-style-type: none"> ○ 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. 	375 mg/m ² IV infusion
Rituxan and rituximab biosimilars	Low-grade and follicular B-cell NHL	<ul style="list-style-type: none"> • Rituxan in combination with Zevalin for low-grade or follicular B-cell NHL: <ul style="list-style-type: none"> ○ 250 mg/m² IV within 4 hrs prior to administration of Indium-111-(In-111-) Zevalin and Yttrium-90-(Y-90) Zevalin. ○ Administer rituximab and In-111-Zevalin 7–9 days prior to rituximab and Y-90-Zevalin. ○ Refer to the Zevalin package insert for full prescribing information regarding the Zevalin therapeutic regimen. 	375 mg/m ² IV infusion

Drug Name	Indication	Dosing Regimen	Maximum Dose
Rituxan Hycela	Follicular B-cell NHL	1,400 mg rituximab and 23,400 units hyaluronidase SC according to the following schedules: <i>First dose must be with IV Rituxan/Truxima if indicated with an asterisk (*).</i> <ul style="list-style-type: none"> • Relapsed or refractory FL: <ul style="list-style-type: none"> ○ Once weekly for 3 or 7 weeks (i.e., 4 or 8 weeks in total)* ○ Retreatment: once weekly for 3 weeks (i.e., 4 weeks in total)* • Previously untreated FL: <ul style="list-style-type: none"> ○ Administer on Day 1 of Cycles 2–8 of chemotherapy (every 21 days), for up to 7 cycles (i.e., up to 8 cycles in total)* ○ If complete/partial response, initiate Rituxan Hycela maintenance treatment as a single-agent every 8 weeks for 12 doses to start 8 weeks following completion of Rituxan Hycela in combination with chemotherapy • Non-progressing FL after first-line CVP chemotherapy: <ul style="list-style-type: none"> ○ Following completion of 6–8 cycles of CVP chemotherapy, administer once weekly for 3 weeks (i.e., 4 weeks in total) at 6 month intervals to a maximum of 16 doses* 	1,400 mg/23,400 units SC per injection
Rituxan and rituximab biosimilars	DLBCL (a B-cell NHL)	375 mg/m ² IV infusion on Day 1 of each cycle of chemotherapy for up to 8 doses total.	375 mg/m ² IV infusion
Rituxan Hycela	DLBCL (a B-cell NHL)	<i>First dose must be with IV Rituxan</i> <ul style="list-style-type: none"> • 1,400 mg rituximab and 23,400 units hyaluronidase SC on Day 1 of Cycles 2–8 of CHOP chemotherapy for up to 7 cycles (i.e., up to 6–8 cycles in total) 	1,400 mg/23,400 units SC per injection
Rituxan and rituximab biosimilars	CLL (a B-cell NHL)	375 mg/m ² IV infusion on the day prior to initiation of FC chemotherapy, then 500 mg/m ² on Day 1 of cycles 2-6 (every 28 days).	500 mg/m ² per day
Rituxan Hycela	CLL (a B-cell NHL)	<i>First dose must be with IV Rituxan</i> <ul style="list-style-type: none"> • 1,600 mg/26,800 units on Day 1 of Cycles 2–6 (every 28 days) for a total of 5 cycles (i.e., 6 cycles in total) 	1,600 mg/26,800 units SC per injection

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Drug Name	Indication	Dosing Regimen	Maximum Dose
Rituxan and rituximab biosimilars	RA	Two 1000 mg IV infusions separated by 2 weeks (i.e., day 1 and day 15), followed by two 1000 mg IV infusions every 16 weeks. Rituxan is given in combination with MTX.	1000 mg per week
Rituxan and rituximab biosimilars	GPA/MPA	<p>Induction:</p> <ul style="list-style-type: none"> 375 mg/m² IV once weekly for 4 weeks in combination with glucocorticoids <p>Follow-up treatment if disease control with induction treatment:</p> <ul style="list-style-type: none"> Two 500 mg IV infusions separated by 2 weeks, followed by 500 mg IV every 6 months thereafter based on clinical evaluation. Follow up treatment should be initiated: <ul style="list-style-type: none"> 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. Within the 4 week period following achievement of disease control if induction was achieved with other immunosuppressants. 	<p>Induction: 375 mg/m² per week</p> <p>Follow-up treatment: 500 mg/dose (see regimen for dosing frequency)</p>
Rituxan and rituximab biosimilars	PV	<p>Initial and maintenance therapy:</p> <ul style="list-style-type: none"> Two 1,000 mg IV infusions separated by 2 weeks with a tapering course of glucocorticoids, then 500 mg IV at month 12 and every 6 months thereafter or based on clinical evaluation <p>Relapse:</p> <ul style="list-style-type: none"> 1,000 mg IV once. Subsequent infusions may be administered no sooner than 16 weeks following the previous infusion. 	<p>Initial/relapse: 1000 mg/dose</p> <p>Maintenance: 500 mg/6 months</p>

VI. Product Availability

Drug Name	Availability
Rituximab (Rituxan)	Single-dose vials for IV injection: 100 mg/10 mL, 500 mg/50 mL
Rituximab-arrx (Riabni)	Single-dose vials for IV injection: 100 mg/10 mL, 500 mg/50 mL
Rituximab-pvvr (Ruxience)	Single-dose vials for IV injection: 100 mg/10 mL, 500 mg/50 mL

Drug Name	Availability
Rituximab-abbs (Truxima)	Single-dose vials for IV injection: 100 mg/10 mL, 500 mg/50 mL
Rituximab-hyaluronidase (Rituxan Hycela)	Single-dose vials for SC injection: 1,400 mg/23,400 units, 1,600 mg/26,800 units

VII. References

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Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-

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date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPSC Codes	Description
J9311	Injection, rituximab 10 mg and hyaluronidase
J9312	Injection, rituximab, 10 mg
Q5115	Injection, rituximab-abbs, biosimilar, (Truxima), 10 mg
Q5119	Injection, rituximab-pvvr, biosimilar, (Ruxience), 10 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
<p>CP.PHAR.148.Rituximab Oncology Hematology policy is incorporated into the present policy (criteria, codes).</p> <p>NHL: The FDA CLL labeled indication is added under NHL. Nodal marginal zone lymphoma is added under NCCN uses. Maximum dose is added. Safety information is removed. Duration is increased to 6 months.</p> <p>RA: modified the RA diagnostic criteria from requiring one or more of the following: ≥ 5 inflamed joints, elevation in the erythrocyte sedimentation rate (ESR) and/or serum C-reactive protein (CRP) concentration; positive rheumatoid factor and/or anticyclic citrullinated peptide (CCP) antibodies (present in most patients), evidence of inflammation on plain radiography of the hands, wrists, or feet, such as osteopenia and/or periarticular swelling to the ACR diagnostic criteria.</p> <p>Safety information is removed.</p> <p>Autoimmune hemolytic anemia (from policy 148): Warm and cold agglutinin disease are combined into one criteria set and edited to reflect rituximab as first-line for cold agglutinin disease and post glucocorticoids for warm agglutinin disease.</p> <p>ICD-10 CM code table updated per NCCN compendia: added C79.32, D36.0, Z85.71, Z85.72, Z85.79</p>	07.17	07.17
<p>2Q 2018 annual review: added HIM line of business; summarized NCCN and FDA approved uses for improved clarity for Non-Hodgkin's Lymphoma; added specialist involvement in care into one criteria set; removed diagnosis requirement for ACR criteria in RA; revised conventional DMARD requirement in RA to require at least one conventional DMARD (e.g., sulfasalazine, leflunomide, hydroxychloroquine); off-label criteria added for additional NCCN-recommended diagnoses; removed off-label criteria for autoimmune hemolytic anemia and immune thrombocytopenia, will instead defer to off-label policy; approval durations updated; references reviewed and updated.</p>	02.27.18	05.18

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Criteria added for new indication for Rituxan: pemphigus vulgaris; myasthenia gravis and nephrotic syndrome diagnoses added to policy as covered diagnoses if off-label criteria is met; references reviewed and updated.	07.31.18	11.18
1Q 2019 annual review: Rituxan biosimilar Truxima is added and applied to all policy criteria applicable to Rituxan; NHL criteria is edited to include all FDA approved or NCCN recommended NHL subtypes; additional NCCN recommended uses other than NHL are added section I.E. (NCCN compendium uses); hematologist added for all oncology indications; GPA/MPA dosing updated to delineate induction versus follow-up treatment and approval duration is edited from 4 weeks total to 6/12 months; PF off-label criteria is added; references reviewed and updated.	01.15.19	02.19
2Q 2019 annual review: updated HCPCS codes; no significant changes; references reviewed and updated.	02.26.19	05.19
RT4: added recently FDA-approved Truxima indication for DLBCL and CLL; references reviewed and updated.	06.06.19	
No significant changes: added general information regarding off-label use in MS.	06.24.19	
Criteria added for off-label use in neuromyelitis optica spectrum disorder; references reviewed and updated.	08.20.19	11.19
RT4: added recently FDA-approved biosimilar Ruxience to all policy criteria applicable to Rituxan.	09.11.19	
Per March SDC and prior clinical guidance, added preferencing for Ruxience; for RA, revised redirection from Enbrel and adalimumab to Inflectra and Renflexis.	03.03.20	
2Q 2020 annual review: removed HIM-Medical Benefit line of business; updated newly approved FDA-indications for Truxina: RA, MPA, GPA; added NCCN 2A supported off-label use primary CNS lymphoma; added requirement for aggressive mature B-cell lymphoma for pediatric patients; added requirement for CD20 positivity for ALL off-label use per NCCN; added preferencing for Ruxience to Section II for continued therapy requests; allowed bypassing of redirection if state regulations do not allow step therapy in Stage IV or metastatic cancer settings references reviewed and updated.	04.20.20	05.20
Added criteria for off-label indication of ITP; for RA, added specific diagnostic criteria for definite RA, baseline CDAI score requirement, and decrease in CDAI score as positive response to therapy. RT4: added Rituxan age expansion to pediatrics ≥ 2 years for GPA and MPA per updated FDA label.	07.22.20	08.20

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
For NMOSD: added requirement against concurrent use with Soliris, Enspryng, or Uplizna; modified EDSS from ≤ 7 to ≤ 8 to align with Uplizna policy; updated HCPCS codes to include Ruxience and Truxima.	07.29.20	11.20
Removed AR from appendix E (“For metastatic cancer, unless the preferred drug is consistent with “best practices” (1) used for treatment under (A) FDA-approved indication, or (B) National Comprehensive Cancer Network Drugs & Biologics Compendium; or (2) using evidence-based, peer-reviewed, recognized medical literature. Note – may not require step therapy a second time for same Rx drug”) to minimize misinterpretation.	11.16.20	
Revised typo in Appendix E from “normal ESR” to “abnormal ESR” for a point gained for ACR Classification Criteria.	11.22.20	
Added criteria for RAPID3 assessment for RA given limited in-person visits during COVID-19 pandemic, updated appendices.	11.24.20	02.21
Updated appendix E to include Ohio.	02.08.21	
Updated GA language in appendix E.	03.10.21	
2Q 2021 annual review: amended biosimilar redirection language to match template update to “must use”; added GVHD (2A) to NCCN Compendium (off-label) section; ensured alignment of biosimilars with Rituxan throughout policy; updated reference for HIM off-label use to HIM.PA.154 (replaces HIM.PHAR.21); RT4: added recently FDA-approved biosimilar Riabni to all policy criteria applicable to Rituxan; added combination of bDMARDs under Section III (less rebate risk than embedding in criteria); updated CDAI table with “>” to prevent overlap in classification of severity; added general information regarding redirection to Ruxience for RA; references reviewed and updated.	02.23.21	05.21

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

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The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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Note:

For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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