Prior Authorization Review Panel

CHC-MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: PA Health & Wellness	**Submission Date: 11/01/2021**
Policy Number: PA.CP.PHAR.260	**Effective Date: 01/2018** **Revision Date: 10/2021**
Policy Name: Rituximab (Rituxan, Ruxience, Truxima, Rituxan Hycela)	

Type of Submission – Check all that apply:

- ☐ **New Policy**
- ✓ **Revised Policy***
- ☐ **Annual Review - No Revisions**
- ☐ **Statewide PDL -** *Select this box when submitting policies for Statewide PDL implementation and when submitting policies for drug classes included on the Statewide PDL.*

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any changes or clarifying information for the policy below:

Per August SDC and prior clinical guidance, modified biosimilar redirection requirements for Rituxan to require use of Ruxience, Truxima, and Riabni in a step-wise manner; modified requirements for Riabni to require use of Ruxience and Truxima; removed age qualification for biosimilar redirection for NHL requests; for continuation of therapy modified age qualification for biosimilar redirection to apply only to GPA or MPA requests; added Commercial line of business (CP.CPA.147 to be retired).

Name of Authorized Individual (Please type or print): **Venkateswara R. Davuluri, MD**	**Signature of Authorized Individual:**

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

Reference Number: PA.CP.PHAR.260
Effective Date: 01/18
Last Review Date: 10/2021

Coding Implications
Revision Log

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*
	Oncology indications (adults)					
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
	Non-progressing (including stable disease), low-grade *[Rituxan, Riabni, Ruxience, Truxima]* or follicular *[Rituxan Hycela],* CD20-positive B-cell NHL as a single agent after first-line CVP chemotherapy	X	X	X	X	X

Indications		Rituxan	Riabni	Ruxience	Truxima	Rituxan Hycela*
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
	Non-oncology indications (adults)					
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 Pennsylvania Health and Wellness® that Rituxan, Riabni, Ruxience, Truxima, and Rituxan Hycela are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Non-Hodgkin's Lymphoma *(includes chronic lymphocytic leukemia)* (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 ≥ 18 years;
   b. Age < 18 years with aggressive mature B-cell lymphoma;
4. If request is for Rituxan or Riabni, member meets one of the following (a, b, or c):
   a. If request is for Rituxan, member must use ALL of the following, unless clinically significant adverse effects are experienced or all are contraindicated (i and ii):
      i. Ruxience and Truxima;
      ii. If member has failed Ruxience and Truxima, then member must use Riabni;
      **Prior authorization may be required for Ruxience, Truxima, and Riabni*
   b. If request is for Riabni, member must use Ruxience and Truxima, unless clinically significant adverse effects are experienced or all are contraindicated;
      **Prior authorization may be required for Ruxience and Truxima*
   c. Request is for Stage IV or metastatic cancer ;
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/m^2 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*).

Approval duration: 6 months

B. Rheumatoid Arthritis (must meet all):
1. Diagnosis of RA per American College of Rheumatology (ACR) criteria (*see Appendix E*);
2. Request is for Rituxan/Riabni/Ruxience/Truxima;
3. Prescribed by or in consultation with a rheumatologist;
4. Age ≥ 18 years;
5. Member meets one of the following (a or b):
   a. Failure of methotrexate (MTX) for ≥ 3 consecutive months at up to maximally indicated does, unless contraindicated or clinically significant adverse effect are experienced;
   b. If intolerance or contraindication to MTX (*see Appendix D*), failure of a ≥ 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 Enbrel® or Humira®, used for ≥ 3 consecutive months, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required for Enbrel or Humira*
7. Documentation of one of the following baseline assessment scores (a or b):
   a. Clinical disease activity index (CDAI) score (*see Appendix F*);
   b. Routine assessment of patient index data 3 (RAPID3) score (*see Appendix G*);

8. If request is for Rituxan or Riabni, member meets one of the following (a or b):
    a. If request is for Rituxan, member must use ALL of the following, unless clinically significant adverse effects are experienced or all are contraindicated (i and ii):
        i. Ruxience and Truxima;
        ii. If member has failed Ruxience and Truxima, then member must use Riabni;
        **Prior authorization may be required for Ruxience, Truxima, and Riabni*
    b. If request is for Riabni, member must use Ruxience and Truxima, unless clinically significant adverse effects are experienced or all are contraindicated;
        **Prior authorization may be required for Ruxience and Truxima*
9. Rituxan/Riabni/Ruxience/Truxima will be administered in combination with MTX unless contraindicated or clinically significant adverse effects are experienced;
10. Prescribed dose does not exceed two-1000 mg infusions separated by 2 weeks followed by two-1000 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 or Riabni, one of the following (a or b):
    a. If request is for Rituxan, member must use ALL of the following, unless clinically significant adverse effects are experienced or all are contraindicated (i and ii):
        i. Ruxience and Truxima;
        ii. If member has failed Ruxience and Truxima, then member must use Riabni;
        **Prior authorization may be required for Ruxience, Truxima, and Riabni*
    b. If request is for Riabni, member must use Ruxience and Truxima, unless clinically significant adverse effects are experienced or all are contraindicated;
        **Prior authorization may be required for Ruxience and Truxima*
6. Prescribed in combination with glucocorticoid therapy (e.g. prednisone, prednisolone, dexamethasone);
7. Dose does not exceed (a or b):
    a. Induction: 375 mg/m^2 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 or Riabni, member meets one of the following (a or b):
    a. If request is for Rituxan, member must use ALL of the following, unless clinically significant adverse effects are experienced or all are contraindicated (i and ii):
        i. Ruxience and Truxima;

ii. If member has failed Ruxience and Truxima, then member must use Riabni;
**Prior authorization may be required for Ruxience, Truxima, and Riabni*

b. If request is for Riabni, member must use Ruxience and Truxima, unless clinically significant adverse effects are experienced or all are contraindicated;
**Prior authorization may be required for Ruxience and Truxima*

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 ≥ 18;
5. If request is for Rituxan or Riabni, member meets one of the following (a, b, or c):
   a. If request is for Rituxan, member must use ALL of the following, unless clinically significant adverse effects are experienced or all are contraindicated (i and ii):
      i. Ruxience and Truxima;
      ii. If member has failed Ruxience and Truxima, then member must use Riabni;
      **Prior authorization may be required for Ruxience, Truxima, and Riabni*
   b. If request is for Riabni, member must use Ruxience and Truxima, unless clinically significant adverse effects are experienced or all are contraindicated;
      **Prior authorization may be required for Ruxience and Truxima*
   c. Request is for Stage IV or metastatic cancer;
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 in consultation with a neurologist;
4. Age ≥ 18 years;
5. Member has experienced at least one relapse within the previous 12 months;
6. If request is for Rituxan or Riabni, member meets one of the following (a or b):
   a. If request is for Rituxan, member must use ALL of the following, unless clinically significant adverse effects are experienced or all are contraindicated (i and ii):
      i. Ruxience and Truxima;

ii. If member has failed Ruxience and Truxima, then member must use Riabni;
**Prior authorization may be required for Ruxience, Truxima, and Riabni*

b. If request is for Riabni, member must use Ruxience and Truxima, unless clinically significant adverse effects are experienced or all are contraindicated;
**Prior authorization may be required for Ruxience and Truxima*

7. Rituxan/Riabni/Ruxience/Truxima is not prescribed concurrently with Soliris®, Enspryng™, or Uplizna®;
8. Request meets one of the following (a, b, or c):
   a. Dose does not exceed 375 mg/m^2 per week for 4 weeks as induction, followed by 375 mg/m^2 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/µL 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 or Riabni, member meets one of the following (a or b):
   a. If request is for Rituxan, member must use ALL of the following, unless clinically significant adverse effects are experienced or all are contraindicated (i and ii):
   iii. Ruxience and Truxima;
   iv. If member has failed Ruxience and Truxima, then member must use Riabni;
   **Prior authorization may be required for Ruxience, Truxima, and Riabni*

   b. If request is for Riabni, member must use Ruxience and Truxima, unless clinically significant adverse effects are experienced or all are contraindicated;
   **Prior authorization may be required for Ruxience and Truxima*
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/m^2 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: Refer to PA.CP.PMN.53

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 or Riabni, member meets one of the following (a, b, or c):
   a. If request is for Rituxan, member must use ALL of the following, unless clinically significant adverse effects are experienced or all are contraindicated (i and ii):
      v. Ruxience and Truxima;
      vi. If member has failed Ruxience and Truxima, then member must use Riabni;
      **Prior authorization may be required for Ruxience, Truxima, and Riabni*
   b. If request is for Riabni, member must use Ruxience and Truxima, unless clinically significant adverse effects are experienced or all are contraindicated;
      **Prior authorization may be required for Ruxience and Truxima*
   c. Request is for Stage IV or metastatic cancer for a State;

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 Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
   b. Documentation supports that member is currently receiving Rituxan, Riabni, Ruxience, Truxima, or Rituxan Hycela for a covered oncology indication;
2. Member is responding positively to therapy;
3. If request is for Rituxan or Riabni, member meets one of the following (a, b, or c):*
   ** For GPA or MPA requests, requirements apply for members ≥ 18 years of age*
   a. If request is for Rituxan, member must use ALL of the following, unless clinically significant adverse effects are experienced or all are contraindicated (i and ii):
      i. Ruxience and Truxima;
      ii. If member has failed Ruxience and Truxima, then member must use Riabni;
      **Prior authorization may be required for Ruxience, Truxima, and Riabni*
   b. If request is for Riabni, member must use Ruxience and Truxima, unless clinically significant adverse effects are experienced or all are contraindicated;
      **Prior authorization may be required for Ruxience and Truxima*
   c. Request is for Stage IV or metastatic cancer;
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 any of the following (a or b):
   d. New dose does not exceed the following:
      i. NHL:
         a) Rituxan/Riabni/Ruxience/Truxima: 500 mg/m^2 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/m^2 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/m^2 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*).

Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2 thru 3):

1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies.
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 (refer to PA.CP.PMN.53):
a. Myasthenia gravis;
b. Nephrotic syndrome;
3. If request is for Rituxan or Riabni, member meets one of the following (a, b, or c):
a. If request is for Rituxan, member must use ALL of the following, unless clinically significant adverse effects are experienced or all are contraindicated (i and ii):
i. Ruxience and Truxima;
ii. If member has failed Ruxience and Truxima, then member must use Riabni;
**Prior authorization may be required for Ruxience, Truxima, and Riabni*
b. If request is for Riabni, member must use Ruxience and Truxima, unless clinically significant adverse effects are experienced or all are contraindicated;
**Prior authorization may be required for Ruxience and Truxima*
c. Request is for Stage IV or metastatic cancer;
4. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

III. 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) *Off-label*	Initial dose: 125 or 250 mg PO QD Maintenance dose: 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®) *Off-label*	Initial dose: 400 – 600 mg/day PO QD Maintenance dose: 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
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
Avsola™, Renflexis™, Inflectra® (infliximab)	In conjunction with MTX Initial dose: 3 mg/kg IV at weeks 0, 2 and 6 Maintenance dose: 3 mg/kg IV every 8 weeks	10 mg/kg every 4 weeks

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks	
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.

Appendix E: 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) *and* negative anti-citrullinated protein antibody (ACPA)	0
	Low positive RF *or* low positive ACPA * *Low: < 3 x upper limit of normal*	2
	High positive RF *or* high positive ACPA * *High: ≥ 3 x upper limit of normal*	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 F: 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 G: 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

IV. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose

Rituxan and rituximab biosimilars	Low-grade and follicular B-cell NHL	375 mg/m^2 IV infusion according to the following schedules:
		• Relapsed or refractory, low-grade or follicular, CD20+, B-cell NHL
		  ○ Once weekly for 4 or 8 doses
		  ○ Retreatment: once weekly for 4 doses
		• Previously untreated, follicular, CD20+, B-cell NHL:
		  ○ 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:
		  ○ 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	• Rituxan in combination with Zevalin for low-grade or follicular B-cell NHL:
		  ○ 250 mg/m^2 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:
		First dose must be with IV Rituxan/Truxima if indicated with an asterisk (*).
		• Relapsed or refractory FL:
		  ○ 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:
		  ○ 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:
		  ○ 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)*	***First dose must be with IV Rituxan*** • 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)*	***First dose must be with IV Rituxan*** • 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

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	Induction: • 375 mg/m^2 IV once weekly for 4 weeks in combination with glucocorticoids Follow-up treatment if disease control with induction treatment: • 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: o 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. o Within the 4 week period following achievement of disease control if induction was achieved with other immunosuppressants.	Induction: 375 mg/m^2 per week Follow-up treatment: 500 mg/dose (see regimen for dosing frequency)
Rituxan and rituximab biosimilars	PV	Initial and maintenance therapy: • 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 Relapse: • 1,000 mg IV once. Subsequent infusions may be administered no sooner than 16 weeks following the previous infusion.	Initial/relapse: 1000 mg/dose Maintenance: 500 mg/6 months

II. 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
Rituximab-abbs (Truxima)	Single-dose vials for IV injection: 100 mg/10 mL, 500 mg/50 mL

Drug Name	Availability
Rituximab-hyaluronidase (Rituxan Hycela)	Single-dose vials for SC injection: 1,400 mg/23,400 units, 1,600 mg/26,800 units

V. References

1. Rituxan Prescribing Information. South San Francisco, CA: Genentech Inc.; August 2020. Available at: https://www.gene.com/download/pdf/rituxan_prescribing.pdf. Accessed January 5, 2021.
2. Riabni Prescribing Information. Thousand Oaks, CA: Amgen, Inc.: December 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761140s000lbl.pdf?utm_medium=email&utm_source=govdelivery. Accessed January 5, 2021.
3. Ruxience Prescribing Information. New York, NY: Pfizer Biosimilars; May 2020. Available at: https://www.ruxience.com/. Accessed January 5, 2021.
4. Truxima Prescribing Information. North Wales, PA: Teva Pharmaceuticals, Inc.; May 2020. Available at: https://www.truximahcp.com. Accessed January 5, 2021.
5. Rituxan Hycela Prescribing Information. South San Francisco, CA: Genentech Inc.; May 2020. Available at: www.rituxanhycela.com. Accessed January 5, 2021.
6. Rituximab. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed January 5, 2021.
7. Singh JA, Saag KG, Bridges SL, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2016; 68(1):1-25. doi: 10.1002/acr.22783. Epub 2015 Nov 6.
8. Buch MH, Smolen JS, Betteridge N, et al. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases*. 2011; 70(6): 909-920.
9. Sellner J, Boggild M, Clanet M, et al. EFNS guidelines on diagnosis and management of neuromyelitis optica. *European Journal of Neurology*. 2010; 17:1019-1032.
10. Kim SH, Huh SY, Lee SJ, et al. A 5-year follow-up of rituximab treatment in patients with neuromyelitis optica spectrum disorder. *JAMA Neurology*. 2013; 70(9):1110-1117.
11. Nikoo Z, Badihian S, Shaygannejag V, Asgari N, Ashtari F. Comparison of the efficacy of azathioprine and rituximab in neuromyelitis optica spectrum disorder: a randomized clinical trial. *J Neurol*. 2017; 264:2003-2009.
12. Gao F, Chai B, Gu C, et al. Effectiveness of rituximab in neuromyelitis optica: a meta-analysis. *BMC Neurology*. 2019; 19(36): 1-7.
13. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv*. 2019;3(23):3829-3866.

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

HCPCS 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	Approval Date
2Q 2018 annual review: 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.	02.27.18	
2Q 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	04.17.19	
2Q 2020 annual review: added recently FDA-approved biosimilar Ruxience to all policy criteria applicable to Rituxan; updated newly approved FDA-indications for Truxima: 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; for RA, removed redirection to adalimumab; Criteria added for off-label use in neuromyelitis optica spectrum disorder; added general information regarding off-label use in MS; references reviewed and updated.	04/2020	
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; for RA, added back redirection to adalimumb; added preferencing for Ruxience; allowed by-passing of redirection for PA regulations that do not allow step therapy in Stage IV or metastatic cancer settings; references reviewed and updated.	07/2020	
For NMOSD: added requirement against concurrent use with Soliris, Enspryng, or Uplizna	10/2020	

Reviews, Revisions, and Approvals	Date	Approval Date
Updated HCPCS codes to include Ruxience and Truxima; added preferencing for Ruxience; clarified Rituxan age expansion to pediatrics ≥ 2 years for GPA and MPA per updated FDA label; added criteria for RAPID3 assessment for RA given limited in-person visits during COVID-19 pandemic	01/2021	
2Q 2021 annual review: added GVHD (2A) to NCCN Compendium (off-label) section; ensured alignment of biosimilars with Rituxan throughout policy; RT4: added recently FDA-approved biosimilar Riabni to all policy criteria applicable to Rituxan; updated CDAI table with ">" to prevent overlap in classification of severity; references reviewed and updated.	04/2021	
Per August SDC and prior clinical guidance, modified biosimilar redirection requirements for Rituxan to require use of Ruxience, Truxima, and Riabni in a step-wise manner; modified requirements for Riabni to require use of Ruxience and Truxima; removed age qualification for biosimilar redirection for NHL requests; for continuation of therapy modified age qualification for biosimilar redirection to apply only to GPA or MPA requests	10/2021	