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

Reference Number: LA.PHAR.260
Effective Date: 04.21
Last Review Date: 0~~1~~4.2~~1~~2
Line of Business: Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Rituximab (Rituxan®) and its biosimilars [rituximab-arrx (Riabni™), rituximab-pvvr (Ruxience™), rituximab-abbs (Truxima®)] are CD20-directed cytolytic antibodies.
~~Rituximab (Rituxan®) is a human monoclonal immunoglobulin G 1 (IgG1) kappa antibody directed against the CD20 antigen.~~

~~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*	X	X	X	X	X

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Indications		Rituxan	Riabni	Ruxience	Truxima	Rituxan Hycela
	Hycela], CD20-positive B-cell NHL as a single agent after first-line CVP chemotherapy					
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	X	
GPA, MPA	GPA and MPA in combination with glucocorticoids	X (2 years and older)	X	X	X	
PV	Moderate to severe PV	X				

Abbreviations: B-AL (B-cell acute leukemia), BL (Burkitt lymphoma), BLL (Burkitt-like lymphoma), 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
Prior authorization required. 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 Louisiana Healthcare Connections that Rituxan, Riabni, Ruxience, Truxima, and Rituxan Hycela are medically necessary when the following criteria are met:

I. Initial Approval Criteria

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

1. Diagnosis of any of the following non-Hodgkin's lymphoma (NHL) subtypes (a-~~m~~n):
   a. AIDS-related B-cell lymphomas;
   b. B-cell acute leukemia;
   ~~a.~~
   ~~b.~~c. Burkitt lymphoma or Burkitt-like lymphoma;

~~c.~~d. Castleman's disease;
~~d.~~e. Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
~~e.~~f. Diffuse large B-cell lymphoma (DLBCL);
~~f.~~g. Follicular lymphoma (FL);
~~g.~~h. Hairy cell leukemia (Rituxan/ Riabni/Ruxience/Truxima only);
~~h.~~i. Low- or high-grade B-cell lymphoma;
~~i.~~j. MALT lymphoma (gastric or nongastric);
~~j.~~k. Mantle cell lymphoma;
~~k.~~l. Marginal zone lymphoma (nodal or splenic);
~~l.~~m. Post-transplant lymphoproliferative disorder;
~~m.~~n. 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, ~~Truxima,~~ member meets one of the following (a, ~~or~~ b or c):
   a. If request is for Rituxan, member must use TWO of the following, unless clinically significant adverse effects are experienced or all are contraindicated (i and ii):
      i. Ruxience or Truxima;
      ii. If member has failed Ruxience or 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;
      ~~a. **Prior authorization may be required for Ruxience and Truxima* Medical justification supports inability to use Ruxience (e.g., contraindications to excipients in Ruxience);~~

      ~~**Prior authorization may be required for Ruxience*~~
   ~~b.~~c. Request is for Stage IV or metastatic cancer or associated conditions. Exception if "clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy.;
5. If request is for Rituxan Hycela, member has received at least one full dose of Rituxan, Riabni, Ruxience, or Truxima;
6. Member does not have combination use with biological disease-modifying antirheumatic drugs or Janus kinase inhibitors (*see Section III: Diagnoses/Indications for which coverage is NOT authorized*);
~~6.~~7. Request meets either of the following (a or b):*
   a. Dose does not exceed the number of cycles as indicated in *Section V* and the following per administration (i or ii):
      i. Rituxan/ Riabni/Ruxience/Truxima: 500 mg/m^2 per IV infusion (*see Section V for cycle regimens)*;

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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 ≥ 18 years;
5. Member meets one of the following (a or b):
   a. Failure of a ≥ 3 consecutive month trial of MTX at up to maximally indicated doses~~, unless contraindicated or clinically significant adverse effects are experienced~~;
   b. Member has~~If~~ intolerance or contraindication to MTX (*see Appendix D*), and 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 or all are contraindicated;
6. Failure of Avsola, Inflectra or Renflexis, unless contraindicated or clinically significant adverse effects are experienced;

   **Prior authorization may be required for Inflectra and Renflexis*

~~7.~~8. 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*);
9. If request is for Rituxan or ~~Truxima~~Riabni, member meets one of the following (a or b): ~~medical justification supports inability to use Ruxience (e.g., contraindications to excipients in Ruxience);~~
   a. If request is for Rituxan, member must use TWO of the following, unless clinically significant adverse effects are experienced or all are contraindicated (i and ii):
      i. Ruxience or Truxima;
      ii. If member has failed Ruxience or 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*

   ~~8.~~
10. Rituxan/ Riabni/Ruxience/Truxima will be administered in combination with MTX unless contraindicated or clinically significant adverse effects are experienced;

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9.11. Member does not have combination use with biological disease-modifying antirheumatic drugs or Janus kinase inhibitors (*see Section III: Diagnoses/Indications for which coverage is NOT authorized*);
10.12. 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 or Riabni~~Truxima~~, one of the following (a or b):
   a. If request is for Rituxan, member must use TWO of the following, unless clinically significant adverse effects are experienced or all are contraindicated (i and ii):
      i. Ruxience or Truxima;
      ii. If member has failed Ruxience or 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*

~~5. medical justification supports inability to use Ruxience (e.g., contraindications to excipients in Ruxience);~~ — **Formatted:** Indent: Left: 0.75", No bullets or numbering

6. Prescribed in combination with a glucocorticoid (e.g. prednisone, prednisolone, dexamethasone);
7. Member does not have combination use with biological disease-modifying antirheumatic drugs or Janus kinase inhibitors (*see Section III: Diagnoses/Indications for which coverage is NOT authorized*);

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7.8. 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 ~~Truxima~~Riabni, member meets one of the following (a or b):
   a. If request is for Rituxan, member must use TWO of the following, unless clinically significant adverse effects are experienced or all are contraindicated (i and ii):
      i. Ruxience or Truxima;
      ii. If member has failed Ruxience or 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;
   ~~5.~~ **Prior authorization may be required for Ruxience and Truxima*~~medical justification supports inability to use Ruxience (e.g., contraindications to excipients in Ruxience);~~
6. Member does not have combination use with biological disease-modifying antirheumatic drugs or Janus kinase inhibitors (*see Section III: Diagnoses/Indications for which coverage is NOT authorized*);

~~6.~~7. 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-f):
   a. Acute lymphoblastic leukemia in patients who are CD20-positive;
   b. Immune checkpoint inhibitor-related toxicities;
   ~~b.~~c. Steroid refractory graft-versus-host disease;
   ~~c.~~d. Leptomeningeal metastases from lymphoma;
   ~~d.~~e. Nodular lymphocyte-predominant Hodgkin lymphoma;
   f. Primary CNS lymphoma;
   ~~e.~~g. Rosai-Dorfman disease;
   ~~f.~~h. 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 years;
5. If request is for Rituxan or Riabni~~Truxima~~, member meets one of the following (a, b, or c):
   a. If request is for Rituxan, member must use TWO of the following, unless clinically significant adverse effects are experienced or all are contraindicated (i and ii):
      i. Ruxience or Truxima;
      ii. If member has failed Ruxience or 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;

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~~5.~~ ~~*Prior authorization may be required for Ruxience and Truxima~~~~member meets one of the following (a or b):~~
~~a. Medical justification supports inability to use Ruxience (e.g., contraindications to excipients in Ruxience);~~
~~*Prior authorization may be required for Ruxience~~
~~b.~~c. Request is for Stage IV or metastatic cancer or associated conditions. Exception if "clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy.;

6. Member does not have combination use with biological disease-modifying antirheumatic drugs or Janus kinase inhibitors (*see Section III: Diagnoses/Indications for which coverage is NOT authorized*);

~~6.~~7. 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. Baseline Expanded Disability Status Scale (EDSS) score ≤ 8;
7. If request is for Rituxan or Riabni~~Truxima~~, member meets one of the following (a or b):
   a. If request is for Rituxan, member must use TWO of the following, unless clinically significant adverse effects are experienced or all are contraindicated (i and ii):
      i. Ruxience or Truxima;
      ii. If member has failed Ruxience or 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;
      ~~7.~~ *Prior authorization may be required for Ruxience and Truxima~~medical justification supports inability to use Ruxience (e.g., contraindications to excipients in Ruxience);~~
8. Rituxan/Riabni/Ruxience/Truxima is not prescribed concurrently with Soliris®, Enspryng™, or Uplizna®;
~~8.~~9. Member does not have combination use with biological disease-modifying antirheumatic drugs or Janus kinase inhibitors (*see Section III: Diagnoses/Indications for which coverage is NOT authorized*);
~~9.~~10. 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;

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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~~Truxima~~, member meets one of the following (a or b):
   a. If request is for Rituxan, member must use TWO of the following, unless clinically significant adverse effects are experienced or all are contraindicated (i and ii):
      i. Ruxience or Truxima;
      ii. If member has failed Ruxience or 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;

   ~~6.~~ **Prior authorization may be required for Ruxience and Truxima*~~medical justification supports inability to use Ruxience (e.g., contraindications to excipients in Ruxience);~~
7. Rituxan/Riabni/Ruxience/Truxima~~Rituximab~~ is not prescribed concurrently with a thrombopoietin receptor agonist (e.g., Nplate®, Promacta®, Doptelet®);
8. Member does not have combination use with biological disease-modifying antirheumatic drugs or Janus kinase inhibitors (*see Section III: Diagnoses/Indications for which coverage is NOT authorized*);

   ~~7.~~
8.9. 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 (must meet all):

1. Member meets one of the following (a or b):

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a. Request is for Stage IV or metastatic cancer or associated conditions. Exception if "clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy.;
b. If request is for Rituxan or Riabni, member meets one of the following (i or ii):
   i. If request is for Rituxan, member must use TWO of the following, unless clinically significant adverse effects are experienced or all are contraindicated (1 and 2):
      a. Ruxience or Truxima;
      b. If member has failed Ruxience or Truxima, then member must use Riabni;
      **Prior authorization may be required for Ruxience, Truxima, and Riabni*
   ii. 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*

2. Member meets one of the following (a or b):
   ~~1.~~a. Members with any of the following diagnoses may be covered if the off-label criteria policy is met:
      ~~i.~~ Myasthenia gravis;
      i.
      ~~b.~~ ii. Nephrotic syndrome;
   ~~2. If request is for Rituxan or Truxima, medical justification supports inability to use Ruxience (e.g., contraindications to excipients in Ruxience);~~
   ~~3.~~b. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): LA.PMN.53 for Medicaid.

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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 Louisiana Healthcare Connections 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 or ~~Truxima~~Riabni, member meets one of the following (a, b or c~~b~~)*:
   ** For GPA or MPA requests, requirements apply for members ≥ 18 years of age*
   a. Request is for Stage IV or metastatic cancer or associated conditions. Exception if "clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy.;
   b. If request is for Rituxan, member must use TWO of the following, unless clinically significant adverse effects are experienced or all are contraindicated (i and ii):
      i. Ruxience or Truxima;
      ii. If member has failed Ruxience or Truxima, then member must use Riabni;
      **Prior authorization may be required for Ruxience, Truxima, and Riabni*
   c. 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*

~~3.~~
~~a. Medical justification supports inability to use Ruxience (e.g., contraindications to excipients in Ruxience);~~
~~**Prior authorization may be required for Ruxience*~~
~~b. Request is for Stage IV or metastatic cancer or associated conditions. Exception if "clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy. ;~~

4. For NMOSD: Rituxan/Riabni/Ruxience/Truxima is not prescribed concurrently with Soliris, Enspryng, or Uplizna;
~~4.~~5. Member does not have combination use with biological disease-modifying antirheumatic drugs or Janus kinase inhibitors (*see Section III: Diagnoses/Indications for which coverage is NOT authorized*);
~~5.~~6. 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)~~1. Rituxan/Riabni/Ruxience/Truxima: 500 mg/m^2 per IV infusion;
         ~~b)~~2. Rituxan Hycela: 1,600 mg/26,800 units per SC injection;

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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*).

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

Approval duration: 12 months

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

~~C.~~

1. Member meets one of the following (a or b):
  a. Request is for Stage IV or metastatic cancer or associated conditions. Exception if "clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy.;
  b. If request is for Rituxan or Riabni, member meets one of the following (i or ii):
    i. If request is for Rituxan, member must use TWO of the following, unless clinically significant adverse effects are experienced or all are contraindicated (1 and 2):
      a. Ruxience or Truxima;
      b. If member has failed Ruxience or Truxima, then member must use Riabni;

      **Prior authorization may be required for Ruxience, Truxima, and Riabni*
    ii. 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*

2. Member meets one of the following (a, b, or c):
  ~~1.~~a. Currently receiving medication via Louisiana Healthcare Connections benefit and documentation supports positive response to therapy. **Approval duration: Duration of request or 6 months (whichever is less)**; or
  ~~2.~~b. Members with any of the following diagnoses may be covered if the off-label criteria policy is met:

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~~a.~~i. Myasthenia gravis;
~~b.~~ii. Nephrotic syndrome;

~~3. If request is for Rituxan or Truxima, medical justification supports inability to use Ruxience (e.g., contraindications to excipients in Ruxience);~~

~~4.~~c. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): LA.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 policy – LA.PMN.53 for Medicaid or evidence of coverage documents.

B. Combination use with biological disease-modifying antirheumatic drugs (bDMARDs) or potent immunosuppressants, including but not limited to any tumor necrosis factor (TNF) antagonists [e.g., Cimzia®, Enbrel®, Humira®, Simponi®, Avsola™, Inflectra™, Remicade®, Renflexis™], interleukin agents [e.g., 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) [e.g., Xeljanz®/Xeljanz® XR, Cibinqo™, Olumiant™, Rinvoq™], anti-CD20 monoclonal antibodies [Rituxan®, Riabni™, Ruxience™, Truxima®, Rituxan Hycela®], selective co-stimulation modulators [Orencia®], and integrin receptor antagonists [Entyvio®] because of the additive immunosuppression, increased risk of neutropenia, as well as increased risk of serious infections.

~~A.~~

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

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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
JAKi: Janus kinase inhibitors

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here 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 Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks	10 mg/kg every 4 weeks
GPA, MPA		
glucocorticoids	Varies	Varies
ITP		

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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 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) *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 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 ~~, Ruxience, Truxima~~	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 o Once weekly for 4 or 8 doses o Retreatment: once weekly for 4 doses • Previously untreated, follicular, CD20+, B-cell NHL: o Administer on Day 1 of each cycle of chemotherapy for up to 8 doses; o 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: o 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

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Drug Name	Indication	Dosing Regimen	Maximum Dose
Rituxan and rituximab biosimilars	Low-grade and follicular B-cell NHL	• Rituxan in combination with Zevalin for low-grade or follicular B-cell NHL: o 250 mg/m^2 IV within 4 hrs prior to administration of Indium-111-(In-111-) Zevalin and Yttrium-90-(Y-90) Zevalin. o Administer rituximab and In-111-Zevalin 7–9 days prior to rituximab and Y-90-Zevalin. o Refer to the Zevalin package insert for full prescribing information regarding the Zevalin therapeutic regimen.	375 mg/m^2 IV infusion
Rituxan	Pediatric patients ≥ 6 months with previously untreated mature B-cell NHL/ B-AL	375 mg/m^2 IV infusion, in combination with cyctemic Lymphone Malin B chemotherapy, given as 2 separate doses during each of the induction courses and one dose during each consolidation course, for a total of 6 infusions	375 mg/m^2 IV infusion

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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: o Once weekly for 3 or 7 weeks (i.e., 4 or 8 weeks in total)* o Retreatment: once weekly for 3 weeks (i.e., 4 weeks in total)* • Previously untreated FL: o 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)* o 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: o 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 ~~Ruxience, Truxima~~	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	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

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Drug Name	Indication	Dosing Regimen	Maximum Dose
biosimilars ~~Ruxience, Truxima~~			
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
Rituxan and rituximab biosimilars ~~Rituxan, Truxima~~	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	Pediatric B-cell NHL/B-AL	375 mg/m^2 IV infusions for a total of 6 doses in combination with Lymphome Malin B chemotherapy (2 doses in first and second induction courses and 1 dose in each consolidation course)	375 mg/m^2 for total 6 doses
Rituxan and rituximab biosimilars ~~Rituxan, Ruxience, Truxima~~	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	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	Initial/relapse: 1000 mg/dose

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Drug Name	Indication	Dosing Regimen	Maximum Dose
biosimilars ~~Rituxan~~		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.	Maintenance: 500 mg/6 months

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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
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

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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-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
Q5123	Injection, rituximab-arrx, biosimilar, (Riabni), 10 mg

Reviews, Revisions, and Approvals	Date	LDH Approval Date
Converted corporate to local policy	01.21	04.21
Added GVHD (2A) to NCCN Compendium (off-label) section; ensured alignment of biosimilars with Rituxan throughout policy; added FDA-approved biosimilar Riabni to all policy criteria applicable to Rituxan; added combination of bDMARDs under Section III; updated CDAI table with ">" to prevent overlap in classification of severity; modified Avsola to parity status with Inflectra and Renflexis; for Ruxience updated FDA approved indications to include RA per updated prescribing information. clarified GVHD use as steroid-refractory; added NCCN-recommended off-label use for Rosai-Dofrman disease; updated existing off-label pediatric mature B-Cell NHL criteria to reflect FDA-approved status; reiterated requirement against combination use with a bDMARD or JAKi from Section III to Sections I and II; references reviewed and updated.	04.22	

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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. LHCC 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.

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 LHCC administrative policies and procedures.

This clinical policy is effective as of the date determined by LHCC. 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. LHCC 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.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom LHCC has no control or right of control. Providers are not agents or employees of LHCC.

This clinical policy is the property of LHCC. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.