Clinical Policy Title:	rituximab, rituximab/hyaluronidase
Policy Number:	RxA.673
Drug(s) Applied:	Riabni™, Rituxan®, Rituxan Hycela®, Ruxience™, Truxima®
Original Policy Date:	03/09/2021
Last Review Date:	03/09/2021
Line of Business Policy Applies to:	All lines of business

Background

Rituximab is a CD20-directed cytolytic antibody, and it is indicated for:

- Adult patients with Non-Hodgkin's Lymphoma (NHL)
  - Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent;
  - Previously untreated follicular, CD20-positive B-cell NHL in combination with first line chemotherapy, and in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as a single agent maintenance therapy;
  - Non-progressing (including stable disease), low-grade, CD20-positive B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy;
  - Previously untreated diffuse large B-cell, CD20-positive NHL, in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens;
- Adult patients with Chronic Lymphocytic Leukemia (CLL)
  - Previously untreated or previously treated CD20-positive CLL, in combination with fludarabine and cyclophosphamide (FC);
- Rheumatoid arthritis (RA), in combination with methotrexate, in adult patients with moderately-to-severely-active RA who have an inadequate response to one or more TNF antagonist therapies;
- Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult and pediatric patients 2 years of age and older, in combination with glucocorticoids; and
- Moderate to severe Pemphigus Vulgaris (PV) in adult patients.

Rituximab-abbs (Truxima®) is indicated for:

- Adult patients with NHL
  - Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as monotherapy
  - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy
  - Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a monotherapy after first-line CVP chemotherapy
  - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens
- Adult patients with CLL
  - Previously untreated and previously treated CD20-positive CLL in combination with FC
- Rheumatoid Arthritis in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies

- GPA and MPA in adult patients in combination with glucocorticoids.

Rituximab-arrx (Riabni™) is indicated for:
- Adult patients with NHL
  - Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as monotherapy;
  - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy;
  - Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as monotherapy after first-line CVP chemotherapy;
  - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens;
- Adult patients with CLL
  - Previously untreated and previously treated CD20-positive CLL in combination with FC; and
- GPA and MPA in adult patients in combination with glucocorticoids.

Rituximab-pvvr (Ruxience™) is indicated for:
- Adult patients with NHL
  - Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as monotherapy;
  - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy;
  - Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a monotherapy after first-line CVP chemotherapy;
  - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens;
- Adult patients with CLL
  - Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC).
- GPA and MPA in adult patients in combination with glucocorticoids.

Rituximab/hyaluronidase is indicated for the treatment of adult patients with:
- Follicular Lymphoma
  - Relapsed or refractory, follicular lymphoma as monotherapy;
  - Previously untreated follicular lymphoma in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single agent maintenance therapy
  - Non-progressing (including stable disease), follicular lymphoma as monotherapy after first-line CVP chemotherapy
- Diffuse Large B-cell Lymphoma (DLBCL)
  - Previously untreated diffuse large B-cell lymphoma in combination with CHOP or other anthracycline-based chemotherapy regimens
- Chronic Lymphocytic Leukemia (CLL)
  - Previously untreated and previously treated CLL in combination with FC

Initiate treatment with rituximab/hyaluronidase only after patients have received at least one full dose of a rituximab product by IV infusion; it is not indicated for the treatment of non-malignant conditions.

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
rituximab Riabni™, Rituxan®, Ruxience™, Truxima®	CLL	The recommended dose is 375 mg/m^2 the day prior to the initiation of FC chemotherapy, then 500 mg/m^2 on day 1 of cycles 2 through 6 (every 28 days).	500 mg/m^2
	GPA/MPA	Induction treatment for active GPA/MPA: Administer rituximab as a 375 mg/m^2 IV infusion once weekly for 4 weeks for patients with active GPA or MPA. Glucocorticoids administered as methylprednisolone 1000 mg IV per day for 1 to 3 days followed by oral prednisone as per clinical practice. This regimen should begin within 14 days prior to or with the initiation of rituximab and may continue during and after the 4 week induction course of rituximab treatment. Follow-up treatment for patients with GPA/MPA who have achieved disease control with induction treatment: Administer rituximab as two-500 mg IV infusions separated by two weeks, followed by 500 mg IV infusion every 6 months thereafter based on clinical evaluation. If induction treatment of active disease was with rituximab, initiate follow-up treatment with rituximab within 24 weeks after the last induction infusion with rituximab or based on clinical evaluation, but no sooner than 16 weeks after the last induction infusion with rituximab. If induction treatment of active disease was with other standard of care immunosuppressants, initiate rituximab follow-up treatment within the 4-week period that follows achievement of disease control. Induction treatment of pediatric patients with active GPA/MPA: Administer rituximab as a 375 mg/m^2 IV infusion once weekly for 4 weeks. Prior to the first rituximab infusion, administer IV methylprednisolone 30 mg/kg (not to exceed 1g/day) once daily for 3 days. Following IV methylprednisolone administration, oral steroids should be continued per clinical practice. Follow up treatment of pediatric patients with GPA/MPA who have achieved disease control with induction treatment: Administer rituximab as two-250 mg/m^2 IV infusions separated by two weeks, followed by a 250 mg/m^2 IV infusion every 6 months thereafter based on clinical evaluation. If induction treatment of active disease was with rituximab, initiate follow up treatment with rituximab within 24 weeks after the last induction infusion with rituximab or based on clinical evaluation, but no sooner than 16 weeks after the last induction infusion with rituximab. If induction treatment of active disease was with other standard of care immunosuppressants, initiate rituximab follow-up treatment within the 4-week period following	375 mg/m^2

		achievement of disease control.	
rituximab Riabni™, Rituxan®, Ruxience™, Truxima®	NHL	375 mg/m^2 as an IV infusion Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL: Administer once weekly for 4 or 8 doses. Retreatment for relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL: Administer once weekly for 4 doses. Previously untreated, follicular, CD20-positive, B-cell NHL: Administer on day 1 of each cycle of chemotherapy for up to 8 doses. In patients with complete or partial response, initiate rituximab maintenance eight weeks following completion of a rituximab product in combination with chemotherapy. Administer rituximab as a monotherapy every 8 weeks for 12 doses Non-progressing, low-grade, CD20-positive, B-cell NHL, after first-line CVP chemotherapy: Following completion of 6 to 8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses. Diffuse large B-cell NHL: Administer on day 1 of each cycle of chemotherapy for up to 8 infusions. Recommended dose as a component of ibritumomab tiuxetan for treatment of NHL: When used as part of the ibritumomab tiuxetan therapeutic regimen, infuse 250 mg/m^2 in accordance with the prescribing information.	375 mg/m^2
	RA	Give in combination with methotrexate. Administer rituximab as two-1000 mg IV infusions separated by 2 weeks. Glucocorticoids administered as methylprednisolone 100 mg IV or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion-related reactions. Subsequent courses should be administered every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks.	1000 mg/ infusion
	PV	Administer rituximab as two-1000 mg IV infusions separated by 2 weeks in combination with a tapering course of glucocorticoids. Maintenance treatment: Administer rituximab as a 500 mg IV infusion at Month 12 and every 6 months thereafter or based on clinical evaluation. Treatment of relapse: Administer rituximab as a 1000 mg IV infusion on relapse and consider resuming or increasing the glucocorticoid dose based on clinical evaluation. Subsequent infusions of rituximab may be administered no sooner than 16 weeks following the previous infusion.	

rituximab/ hyaluronidase (Rituxan Hycela®)	CLL	All patients must receive at least one full dose of a rituximab product by IV infusion before starting treatment with rituximab/hyaluronidase. Premedicate before each dose. The recommended dose for CLL is 1,600 mg rituximab and 26,800 units hyaluronidase in combination with FC chemotherapy, at a fixed dose, irrespective of patient's body surface area. Administer rituximab/hyaluronidase 1,600 mg/26,800 units on day 1 of cycles 2 through 6 (every 28 days) for a total of 5 cycles following a full IV dose of rituximab at day 1 of cycle 1 (i.e., 6 cycles in total).	1,600 mg rituximab and 26,800 units hyaluronidase
	DLBCL	All patients must receive at least one full dose of a rituximab product by IV infusion before starting treatment with rituximab/hyaluronidase. Premedicate before each dose. The recommended dose for DLBCL is 1,400 mg rituximab and 23,400 units hyaluronidase at a fixed dose irrespective of patient's body surface area in combination with CHOP chemotherapy. Administer rituximab/hyaluronidase 1,400 mg/23,400 units on day 1 of cycles 2 through 8 of CHOP chemotherapy for up to 7 cycles following a full dose of rituximab by IV infusion at day 1 of cycle 1 of CHOP chemotherapy (i.e., up to 6–8 cycles in total).	1,400 mg rituximab and 23,400 units hyaluronidase
	Follicular Lymphoma	All patients must receive at least one full dose of a rituximab product by IV infusion before starting treatment with rituximab/hyaluronidase. Premedicate before each dose. The recommended dose is 1,400 mg rituximab and 23,400 units hyaluronidase SQ at a fixed dose irrespective of patient's body surface area according to the following schedules: Relapsed or refractory follicular Lymphoma: Administer once weekly for 3 or 7 weeks following a full dose of rituximab by IV infusion at week 1 (i.e., 4 or 8 weeks in total). Retreatment for relapsed or refractory follicular lymphoma: Administer once weekly for 3 weeks following a full dose of rituximab by IV infusion at week 1 (i.e., 4 weeks in total). Previously untreated follicular lymphoma: Administer on day 1 of cycles 2–8 of chemotherapy (every 21 days), for up to 7 cycles following a full dose of rituximab by IV infusion on day 1 of cycle 1 of chemotherapy (i.e., up to 8 cycles in total). In patients with complete or partial response, initiate rituximab/hyaluronidase maintenance treatment 8 weeks following completion of rituximab/hyaluronidase in combination with chemotherapy. Administer rituximab/hyaluronidase as monotherapy every 8 weeks for 12 doses. Non-progressing follicular lymphoma after first line CVP	

		chemotherapy: Following completion of 6–8 cycles of CVP chemotherapy and a full dose of rituximab by IV infusion at week 1, administer once weekly for 3 weeks (i.e., 4 weeks in total) at 6-month intervals to a maximum of 16 doses.	

Dosage Forms

Rituximab (all products):

- Injection, single-dose vials: 100 mg/10 mL, 500 mg/50 mL

Rituximab/hyaluronidase:

- Injection, single-dose vials: 1,400 mg rituximab and 23,400 units hyaluronidase per 11.7 mL (120 mg/2,000 Units per mL) and 1,600 mg rituximab and 26,800 units hyaluronidase per 13.4 mL (120 mg/2,000 Units per mL)

Clinical Policy

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

I. Initial Approval Criteria

A. Autoimmune mucocutaneous blistering disease (e.g., pemphigus vulgaris, pemphigus foliaceus) (must meet all):

1. Member has a diagnosis of moderate to severe PV or PF;
2. Prescribed by or in consultation with a dermatologist;
3. Member is 18 years of age or older;
4. Prescribed in combination with a tapering course of glucocorticoids;
5. Dose does not exceed FDA prescribing guidelines.

Approval Duration
Commercial: Up to 6 months
Medicaid: Up to 6 months

B. Granulomatosis with Polyangiitis (Wegener's Granulomatosis)/Microscopic Polyangiitis (MPA) (must meet all):

1. Member has a diagnosis of GPA or MPA;
2. Prescribed by or in consultation with an rheumatologist;
3. Member is 2 years of age or older;
4. Rituximab is prescribed in combination with glucocorticoids or the member has a contraindication or intolerance to glucocorticoids;
5. For requests other than Ruxience™: Member must have tried and failed Ruxience™, at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed FDA prescribing guidelines.

Approval Duration
Commercial: 3 months
Medicaid: 3 months

C. Non-Hodgkin's Lymphoma (must meet all):

1. Member has one of the following diagnoses (a, b, or c):
   a. Castleman's disease;
   b. CLL/SLL;
   c. One of the following CD20-positive B-cell NHL diagnoses (i-xiii):
      i. AIDS-related B-cell lymphoma;
      ii. B-cell lymphoblastic lymphoma;
      iii. Burkitt lymphoma;
      iv. Diffuse large B-cell lymphoma;
      v. Follicular lymphoma;
      vi. Hairy cell leukemia;
      vii. Histological transformation from nodal marginal zone lymphoma to DLBCL;
      viii. Low- or high-grade B-cell lymphomas;
      ix. MALT lymphoma (gastric or non-gastric);
      x. Mantle cell lymphoma;
      xi. Marginal zone lymphoma (nodal or splenic);
      xii. PTLD;
      xiii. Primary cutaneous B-cell lymphoma;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Member is 18 years of age or older for all diagnoses except for pediatric aggressive mature B-cell lymphoma;
4. For requests other than Ruxience™ (except Rituxan Hycela®): Member must have tried and failed Ruxience™, at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. For Rituxan Hycela® requests, member must have received at least one full dose of rituximab;
6. Dose does not exceed FDA prescribing guidelines.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

D. Rheumatoid arthritis (must meet all):

1. Member has a diagnosis of moderate-to-severe active RA;
2. Prescribed by or in consultation with a rheumatologist;
3. Member is 18 years of age or older;
4. Member has failed at least one anti-TNF therapy (e.g., adalimumab, etanercept);
5. Prescribed in combination with methotrexate unless member has a contraindication or intolerance to methotrexate;
6. Baseline clinical disease activity index (CDAI) score is documented;
7. Member is not receiving rituximab in combination with other biologic DMARDs (e.g., etanercept, adalimumab, certolizumab, golimumab) or Janus kinase inhibitors (e.g., tofacitinib);
8. Dose does not exceed FDA prescribing guidelines.

Approval Duration
Commercial: Up to 6 months
Medicaid: Up to 6 months

E. Autoimmune hemolytic anemia (off-label) (must meet all):
1. Member has a diagnosis of autoimmune hemolytic anemia;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Member is 18 years of age or older;
4. For requests other than Ruxience™: Member must have tried and failed Ruxience™, at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration
Commercial: Up to 3 months
Medicaid: Up to 3 months

F. Immune thrombocytopenic purpura (off-label) (must meet all)**:**
1. Member has a diagnosis of ITP;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Member is 18 years of age or older;
4. Documented platelet count less than 50 x 10^9/L;
5. History of failure, contraindication, or intolerance to the following therapies:
   a. Immune globulins;
   b. Glucocorticoids;
   c. Splenectomy;
6. For requests other than Ruxience™: Member must have tried and failed Ruxience™, at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
7. Dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration
Commercial: Up to 6 months
Medicaid: Up to 6 months

G. Immunotherapy-related encephalitis (off-label) (must meet all):
1. Member has a diagnosis of immunotherapy-related encephalitis;
2. Prescribed by or in consultation with a neurologist, oncologist, or infectious disease specialist;
3. Member is 18 years of age or older;
4. Member meets one of the following (a or b):
   a. Member has had limited improvement after glucocorticoid therapy for a minimum of 7 days unless the member has a contraindication or intolerance to glucocorticoids; or
   b. Member has autoimmune encephalopathy and infectious causes of encephalitis have been ruled out;
5. Member has had recent immunotherapy with a checkpoint inhibitor (e.g., atezolizumab, nivolumab, pembrolizumab) unless member has a contraindication or intolerance to such therapy;
6. For requests other than Ruxience™: Member must have tried and failed Ruxience™, at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
7. Dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration
Commercial: Up to 3 months
Medicaid: Up to 3 months

H. Multiple sclerosis (off-label) (must meet all):
1. Member has one of the following diagnoses (a or b):
   a. Primary progressive MS;
   b. Relapsing forms of MS (e.g., relapsing-remitting, secondary-progressive MS with relapses, progressive-relapsing MS);
2. Prescribed by or in consultation with a neurologist;
3. Member is 18 years of age or older;
4. Member is not receiving disease modifying therapy (e.g., interferon beta preparations, dimethyl fumarate, fingolimod, glatiramer, natalizumab, Siponimod, teriflunomide), B-cell targeted therapy (e.g., belimumab, ocrelizumab, ofatumumab), or lymphocyte trafficking blockers (e.g., alemtuzumab, mitoxantrone);
5. For requests other than Ruxience™: Member must have tried and failed Ruxience™, at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration
Commercial: Up to 6 months
Medicaid: Up to 6 months

I. Neuromyelitis optica (off-label) (must meet all):
1. Member has a diagnosis of neuromyelitis optica spectrum disorder (NMOSD) confirmed by the following:
   a. Serologic testing for anti-aquaporin-4 immunoglobulin G (AQP 4-IgG)/NMO-IgG antibodies;
   b. Past medical history of (if AQP 4-IgG/NMO-IgG positive, one of the following; if negative, two of the following) (i, ii, iii, iv, v, or vi):
      i. Acute brainstem syndrome;
      ii. Acute myelitis;
      iii. Area postrema syndrome;
      iv. Optic neuritis;
      v. Symptomatic cerebral syndrome with NMOSD-typical brain lesions;
      vi. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions;
   c. Diagnosis of multiple sclerosis or other diagnoses have been ruled out;
2. Prescribed by or in consultation with a neurologist;
3. Member is 18 years of age or older;
4. Member has tried and failed or has a contraindication or intolerance to at least two of the following (a, b, or c):
   a. Azathioprine;
   b. Glucocorticoids;
   c. Mycophenolate mofetil;
5. Member is not receiving other disease modifying therapies for multiple sclerosis (e.g., dimethyl fumarate, fingolimod, ocrelizumab), anti-IL6 therapies (e.g., tocilizumab), or complement inhibitors (e.g., eculizumab);
6. For requests other than Ruxience™: Member must have tried and failed Ruxience™, at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
7. Dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration

Commercial: Up to 6 months
Medicaid: Up to 6 months

J. Other Cancer diagnoses (off-label) (must meet all):
1. Member has one of the following diagnoses (a, b, c, d, or e):
   a. Acute lymphoblastic leukemia in patients who are CD20-positive;
   b. B-cell NHL (not CD20-positive);
   c. Leptomeningeal metastases (from lymphoma);
   d. Nodular lymphocyte-predominant Hodgkin's lymphoma;
   e. Primary CNS lymphoma;
   f. Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Member is 18 years of age or older;
4. For requests other than Ruxience™ (except Rituxan Hycela®): Member must have tried and failed Ruxience™, at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
8. For Rituxan Hycela® requests, member must have received at least one full dose of rituximab;
9. Dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

K. Thrombotic thrombocytopenic purpura (off-label) (must meet all):
1. Member has a diagnosis of TTP;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Member is 18 years of age or older;
4. Rituximab is being prescribed in combination with plasma exchange therapy;
5. Prescribed in combination with glucocorticoids unless member has a contraindication or intolerance to glucocorticoids;
6. For requests other than Ruxience™: Member must have tried and failed Ruxience™, at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
7. Dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration
Commercial: Up to 3 months
Medicaid: Up to 3 months

II. Continued Therapy Approval

A. Autoimmune mucocutaneous blistering disease (e.g., pemphigus vulgaris Lymphoma (must meet all):
1. Member is currently receiving the medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is positively responding to therapy;
3. If request is for a dose increase, dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration
Commercial: Up to 12 months
Medicaid: Up to 12 months

B. Granulomatosis with Polyangiitis (Wegener's Granulomatosis)/Microscopic Polyangiitis (MPA) (must meet all):

1. Member is currently receiving the medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is positively responding to therapy;
3. Member continues to receive glucocorticoids unless member has a contraindication or intolerance to glucocorticoids;
4. If request is for a dose increase, dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration
Commercial: Up to 12 months
Medicaid: Up to 12 months

C. Non-Hodgkin's Lymphoma (must meet all):

1. Member is currently receiving the medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is positively responding to therapy;
3. If request is for a dose increase, dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration
Commercial: Up to 12 months
Medicaid: Up to 12 months

D. Rheumatoid arthritis (must meet all):

1. Member is currently receiving the medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is positively responding to therapy;
3. Member continues to receive methotrexate unless member has a contraindication or intolerance to methotrexate;
4. If request is for a dose increase, dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration
Commercial: Up to 12 months
Medicaid: Up to 12 months

E. Autoimmune hemolytic anemia (off-label) (must meet all):

1. Member is currently receiving the medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is positively responding to therapy;
3. If request is for a dose increase, dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration
Commercial: 3 months
Medicaid: 3 months

F. Immune thrombocytopenic purpura (off-label) (must meet all):

1. Member is currently receiving the medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is positively responding to therapy;
3. If request is for a dose increase, dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration
Commercial: Up to 12 months
Medicaid: Up to 12 months

G. Immunotherapy-related encephalitis (off-label)

1. No extension of authorization is permitted.

H. Multiple sclerosis (off-label) (must meet all):

1. Member is currently receiving the medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is positively responding to therapy;
3. Member is not receiving disease modifying therapy (e.g., interferon beta preparations, dimethyl fumarate, fingolimod, glatiramer, natalizumab, Siponimod, teriflunomide), B-cell targeted therapy (e.g., belimumab, ocrelizumab, ofatumumab), or lymphocyte trafficking blockers (e.g., alemtuzumab, mitoxantrone);
4. If request is for a dose increase, dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration
Commercial: Up to 12 months
Medicaid: Up to 12 months

I. Neuromyelitis optica (off-label) (must meet all):

1. Member is currently receiving the medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is positively responding to therapy demonstrated by the following:
   a. Reduction in the number and/or severity of relapses or signs/symptoms of NMOSD;
   b. Maintenance, dose reduction, or discontinuation of any baseline immunosuppressive therapy prior to starting rituximab. Note: Add on, dose escalation of immunosuppressive therapy, or additional rescue therapy from baseline to treat NMOSD or exacerbation of symptoms while on rituximab therapy will be considered as treatment failure;
3. Member is not receiving other disease modifying therapies for multiple sclerosis (e.g., dimethyl fumarate, fingolimod, ocrelizumab), anti-IL6 therapies (e.g., tocilizumab), or complement inhibitors (e.g., eculizumab);
4. If request is for a dose increase, dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration
Commercial: Up to 12 months
Medicaid: Up to 12 months

J. Other Cancer diagnoses (off-label) (must meet all):

1. Member is currently receiving the medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is positively responding to therapy;
3. If request is for a dose increase, dose does not exceed FDA prescribing guidelines or dosing is supported by evidence-based guidelines or peer-reviewed literature for the relevant off-label use.

Approval Duration
Commercial: Up to 12 months
Medicaid: Up to 12 months

K. Thrombotic thrombocytopenic purpura (off-label)

1. No extension of authorization is permitted.

III. Appendices

APPENDIX A: Abbreviation/Acronym Key

CDAI: Clinical Disease Activity Index
CHOP: Cyclophosphamide, doxorubicin, vincristine, and Prednisone chemotherapy
CLL: Chronic Lymphocytic Leukemia
CNS: Central Nervous System
CVP: Cyclophosphamide, Vincristine, and Prednisone chemotherapy
DLBCL: Diffuse Large B-Cell Lymphoma
DMARD: Disease-Modifying Anti-Rheumatic Drug
FC: Fludarabine and Cyclophosphamide
FDA: Food and Drug Administration
GPA: Granulomatosis with Polyangiitis
ITP: Immune Thrombocytopenic Purpura
IV: Intravenous/intravenously
MALT: Mucosa-Associated Lympohoid Tissue
MPA: Microscopic Polyangiitis
MS: Multiple Sclerosis
NCCN: National Comprehensive Cancer Network
NHL: Non-Hodgkin's Lymphoma
NMOSD: Neuromyelitis Optica Spectrum Disorder
PCP: Pneumocystis jirovecii pneumonia
PF: Pemphigus Foliaceus
PTLD: Post-Transplant B-Lymphoproliferative Disorder
PV: Pemphigus Vulgaris
RA: Rheumatoid Arthritis
SLL: Small Lymphocytic lymphoma
SQ: Subcutaneous/subcutaneously
TNF: Tumor Necrosis Factor
TTP: Thrombotic Thrombocytopenic Purpura

APPENDIX B: Therapeutic Alternatives

Not applicable

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - None

- Boxed Warning(s):
  Rituximab:
  - Fatal infusion-related reactions have occurred within 24 hours of rituximab infusion. Approximately 80% of fatal reactions occurred with the first infusion. Monitor patients and discontinue infusion if severe reactions occur.
  - Severe mucocutaneous reactions, some with fatal outcomes, have been reported.
  - Hepatitis B virus reactivation may occur resulting in fulminant hepatitis, hepatic failure, or death.
  - Progressive multifocal leukoencephalopathy resulting in death has been reported.

  Rituximab/hyaluronidase:
  - Severe mucocutaneous reactions, some with fatal outcomes, have been reported.
  - Hepatitis B virus reactivation may occur resulting in fulminant hepatitis, hepatic failure, or death.
  - Progressive multifocal leukoencephalopathy resulting in death has been reported.

APPENDIX D: General Information

- Rituximab should only be administered as an IV infusion; do not administer as an IV push or bolus.
- Screen all patients for Hepatitis B virus infection.
- Warnings and precautions:
  - Administer aggressive intravenous hydration, anti-hyperuricemic agents, and monitor renal function to mitigate tumor lysis syndrome.
  - Withhold rituximab and institute appropriate anti-infective therapy if patient has active infection.
  - Discontinue infusions in case of serious or life-threatening cardiovascular events.
  - Discontinue in patients with rising serum creatinine or oliguria.
  - Consider and evaluate for abdominal pain, vomiting, or related symptoms for possible bowel obstruction or perforation.
  - Live virus vaccinations prior to or during rituximab treatment is not recommended.
  - Rituximab ca cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception.
- Common adverse reactions:
  - CLL (25% or greater): infusion-related reactions and neutropenia
  - GPA and MPA (15 % or greater): infections, nausea, diarrhea, headache, muscle spasms, anemia, peripheral edema, and infusion-related reactions
  - NHL (25% or greater): infusion-related reactions, fever, lymphopenia, chills, infection, and asthenia
  - PV (15% or greater): infusion-related reactions, depression, upper respiratory tract infection/ nasopharyngitis, and headache
  - RA (10% or greater): upper respiratory tract infection, nasopharyngitis, urinary tract infection, and bronchitis. Other important adverse reactions include infusion-related reactions, serious infections, and cardiovascular events.
- Recommended dose for premedication and prophylactic medications for rituximab infusions:
  - Premedicate with acetaminophen and an antihistamine before each infusion.
  - For patients administered rituximab according to the 90-minute infusion rate, the glucocorticoid component of their chemotherapy regimen should be administered prior to infusion. For RA, GPA/MPA, and PV patients: Methylprednisolone 100 mg IV or its equivalent is recommended 30 minutes prior to each infusion.
  - Provide prophylaxis treatment for Pneumocystis jirovecii pneumonia (PCP) and herpes virus infections

for patients with CLL during treatment and for up to 12 months following treatment as appropriate. PCP prophylaxis is also recommended for patients with GPA and MPA during treatment and for at least 6 months following the last infusion. PCP prophylaxis should be considered for patients with PV during and following rituximab treatment.

- Recommended dose for premedication and prophylactic medications for rituximab/hyaluronidase:
  - Premedicate with acetaminophen and an antihistamine before each dose.
  - Premedication with a glucocorticoid should also be considered.
  - Provide prophylaxis PCP and herpes virus infections for patients with CLL during treatment and for up to 12 months following treatment as appropriate.

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