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Subject: Rituximab Products [rituximab (Rituxan®), rituximab-abbs(Truxima®), rituximab-pvvr (Ruxience™), and rituximab;hyaluronidase (Rituxan Hycela™)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Rituximab (Rituxan®) is a chimeric monoclonal antibody that targets CD20, which is primarily located on the surface of immune system B cells. Once rituximab binds to CD20, B-cells are destroyed; consequently, rituximab is used to treat diseases that are characterized by excessive amounts of B cells, by overactive B cells, or by dysfunctional B cells. Examples include lymphomas, leukemias, autoimmune disorders and in transplant rejection.

Rituximab was initially approved by the US Food and Drug Administration (FDA) in November 1997 for the treatment of relapsed or refractory B-cell Non-Hodgkin's Lymphoma (NHL). Additional FDA-labeled indications include Chronic Lymphocytic Leukemia (CLL), rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis)/microscopic polyangiitis (MPA), and moderate to severe pemphigus vulgaris (PV). Standard reference compendia (e.g., Clinical Pharmacology, DrugDex) support rituximab use in a plethora of off-label indications include autoimmune blistering diseases, autoimmune hemolytic anemia, neuromyelitis optica, and many more. Two biosimilar forms of rituximab have been FDA approved: rituximab-abbs (Truxima®) and rituximab-pvvr (Ruxience™).

Rituximab;hyaluronidase (Rituxan Hycela™) was FDA approved in June 2017 for adult patients with follicular lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia. Rituximab;hyaluronidase is administered subcutaneously and is only recommended following an initial dose of intravenous rituximab. It is not indicated for the treatment of non-malignant conditions.

Hyaluronidase increases the permeability of subcutaneous tissue by temporarily depolymerizing hyaluronan, a polysaccharide in subcutaneous tissue. This results in dispersion and absorption of rituximab when administered subcutaneously in combination with hyaluronidase. Rituximab;hyaluronidase has demonstrated non-inferior trough concentrations and comparable efficacy and safety to intravenous rituximab.

POSITION STATEMENT:

1. **Initiation** of rituximab (Rituxan®), rituximab-abbs (Truxima®), or rituximab-pvvr (Ruxience™) **meets the definition of medical necessity** when administered for the indications listed in Table 1 and **ALL** of the indication-specific and maximum-allowable dose criteria are met:

Table 1

Indications and Specific Criteria		
Indication	**Specific Criteria**	**Maximum Allowable Dose**
Non-oncology related		
Autoimmune blistering disease (**ANY** of the following) • Pemphigus vulgaris • Pemphigus foliaceus • Bullous pemphigoid • Cicatricial pemphigoid • Epidermolysis bullosa acquisita • Paraneoplastic pemphigus	Member meets **ONE** of the following: 1. **BOTH** of the following are met: a. Member had an inadequate response to corticosteroids b. Member had an inadequate response to oral immunosuppressant therapy including **ONE** or more of the following: i. Mycophenolate ii. Azathioprine iii. Cyclosporine iv. Methotrexate 2. Member is diagnosed with moderate to severe pemphigus vulgaris	375 mg/m^2 per dose*
Autoimmune hemolytic anemia, cold type (AIHA)	Diagnosis only	375 mg/m^2 per dose
AIHA, warm type	When the member had an inadequate response to a trial of corticosteroids (e.g., prednisone 1 mg/kg/day for 3 weeks)	375 mg/m^2 per dose

Castleman's Disease	Member meets **ONE** of the following: 1. Diagnosis of Multicentric Castleman's Disease 2. Unicentric Castleman's Disease and ONE of the following is met: a. Disease is surgically unresectable b. Member is symptomatic following incomplete/partial resection c. Disease is relapsed or refractory	375 mg/m^2 per dose
Evan's syndrome	Documented inadequate response, contraindication, or intolerance to conventional therapy (e.g.,corticosteroids, azathioprine, cyclophosphamide, cyclosporine)	375 mg/m^2 per dose
Graft versus host disease, chronic (GVHD)	When **BOTH** of the following are met: 1. Member had an inadequate response to corticosteroids 2. Member had an inadequate response to immunosuppressants (e.g., cyclosporine, tacrolimus, sirolimus)	375 mg/m^2 per dose
Heart transplant	When the member is receiving therapy for **ONE** of the following: 1. Desensitization for highly-allosensitized transplant candidates 2. Anti-body mediated rejection (AMR)	375 mg/m^2 per dose
Hemophilia, acquired factor inhibitors	When the member has an inadequate response or contraindication to **ONE** of the following: 1. Adequate trial of corticosteroids or cyclophosphamide (e.g., 4-6 weeks) 2. Immune tolerance induction therapy	375 mg/m^2 per dose
Idiopathic or immune thrombocytopenic purpura, chronic (ITP)	When the member is at risk of bleeding and **BOTH** of the following are met: 1. The member has demonstrated an inadequate response to **ANY** of the following: a. Adequate trial of corticosteroids (e.g., prednisone 1-2 mg/kg for 2-4 weeks) b. IVIG c. Splenectomy 2. Member's platelet count is less than 30,000	375 mg/m^2 per dose

Myasthenia Gravis, refractory	When the member has progressive disease with an inadequate response, contraindication, or intolerance to **ALL** of the following: 1. pyridostigmine 2. corticosteroids 3. azathioprine 4. cyclosporine 5. IVIG	375 mg/m^2 per dose
Neuromyelitis optica (NMO)	When the member had an inadequate response to a trial (e.g., 3 months) of one or more of the following oral immunosuppressants: 1. Azathioprine 2. Methotrexate 3. Mycophenolate	1000 mg administered on day 1 and 15 every 24 weeks
Pediatric idiopathic nephrotic syndrome	When **BOTH** of the following are met: 1. Member's disease is dependent on or refractory to corticosteroids 2. Member had an inadequate response to oral immunosuppressant therapy (e.g., tacrolimus, cyclosporine, mycophenolate)	375 mg/m^2 per dose
Relapsing-Remitting Multiple Sclerosis (RRMS)	When **ALL** of the following are met: 1. Member is diagnosed with a relapsing form of multiple sclerosis (i.e., relapsing remitting multiple sclerosis [RRMS], secondary progressive MS [SPMS], progressive-relapsing MS [PRMS]). 2. The member has an inadequate response to **TWO** of the following: a. Alemtuzumab (Lemtrada) b. Cladribine (Mavenclad) c. Dimethyl fumarate (Tecfidera) d. Fingolimod (Gilenya) e. Glatiramer acetate (Copaxone, Glatopa) f. Interferon beta-1a (Avonex, Rebif) g. Interferon beta-1b (Betaseron, Extavia) h. Natalizumab (Tysabri) i. Ocrelizumab (Ocrevus)	1000 mg administered on day 1 and 15 every 24 weeks

	j. Peg-interferon beta-1a (Plegridy) k. Siponimod (Mayzent) l. Teriflunomide (Aubagio) 3. Rituximab will not be used in combination with **ANY** of the following: a. Alemtuzumab (Lemtrada) b. Cladribine (Mavenclad) c. Dimethyl fumarate (Tecfidera) d. Fingolimod (Gilenya) e. Glatiramer acetate (Copaxone, Glatopa) f. Interferon beta-1a (Avonex, Rebif) g. Interferon beta-1b (Betaseron, Extavia) h. Mitoxantrone (Novantrone) i. Natalizumab (Tysabri) j. Ocrelizumab (Ocrevus) k. Peg-interferon beta-1a (Plegridy) l. Siponimod (Mayzent) m. Teriflunomide (Aubagio)	
Renal Transplant	When used to prevent graft rejection in members with anti-donor antibodies (e.g., anti-HLA antibodies)	375 mg/m^2 per dose
Rheumatoid Arthritis (RA)	When **ALL** of the following are met: 1. Member's disease is moderately to severely active 2. Rituximab will be used in combination with methotrexate (unless member has a contraindication to methotrexate) 3. Member is 18 years of age or older 4. Member has at least ONE of the following: A. Member has an inadequate response to a trial (e.g., 3 months) of one or more of the following biologic therapies: a. Adalimumab (Humira) b. Abatacept (Orencia) c. Certolizumab Pegol (Cimzia) d. Etanercept (Enbrel) e. Golimumab (Simponi, Simponi Aria)	1000 mg administered on day 1 and 15 every 16 weeks

	f. Infliximab (Remicade) g. Tocilizumab (Actemra) B. Member has a history of treated lymphoproliferative malignancy	
Systemic autoimmune diseases	When the member is diagnosed with **ONE** of the following: 1. Cryoglobulinemia 2. Primary Sjögren Syndrome	375 mg/m^2 per dose
Systemic Lupus Erythematosus	When the member has **ONE** of the following: 1. The member has an inadequate response or has a contraindication to at least 2 immunosuppressants (e.g., mycophenolate mofetil, cyclophosphamide, azathioprine) 2. The member has nephritis that has an inadequate response to a trial of immunosuppressant therapy (e.g., 6 months)	375 mg/m^2 per dose
Thrombotic thrombocytopenic purpura (TTP)	When the member has an inadequate response to plasma exchange and corticosteroids	375 mg/m^2 per dose
Vasculitides • Granulomatosis with Polyangiitis (GPA or Wegener's granulomatosis) • Churg-Strauss syndrome • Microscopic polyangiitis (MPA) • Pauci-immune glomerulonephritis	When rituximab will be used in combination with corticosteroids	375 mg/m^2 per dose
Oncology-related		
Acute lymphoblastic leukemia (ALL)	When the member has CD20 positive disease and **ONE** of the following are met: 1. ALL is Philadelphia chromosome negative (Ph-) and rituximab is used with **ONE** of the following: a. GRAALL-2005 regimen (daunorubicin, vincristine, prednisone, pegaspargase, and cyclophosphamide) b. HyperCVAD (hyper-fractionated	375 mg/m^2 per dose

	cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine c. GMALL regimen (Idarubicin, dexamethasone, vincristine, cyclophosphamide and cytarabine) d. MOpAD regimen (methotrexate, vincristine, pegaspargase, dexamethasone) 2. ALL is Philadelphia chromosome positive (Ph+) and all of the following are met: a. Member has relapsed or refractory disease b. Member's ALL is refractory to tyrosine kinase inhibitors c. Use is in combination with MOpAD regimen (methotrexate, vincristine, pegaspargase, dexamethasone)	
Central nervous system (CNS) Cancer - Leptomeningeal Metastases	Rituximab will be administered intrathecally in members who meet **ONE** of the following: 1. Used as primary treatment in members with normal CSF flow 2. Used as maintenance therapy for members with negative CSF cytology 3. Used as treatment in members with positive CSF cytology	25 mg per dose
Central nervous system (CNS) Cancers – Primary CNS Lymphoma	When **ONE** of the following is met: 1. For induction or consolidation therapy in combination with **EITHER**: a. High-dose methotrexate, vincristine, procarbazine b. High-dose methotrexate with or without temozolomide 2. For relapsed or refractory disease when used as a single agent or in combination with **ONE** of the following: a. Temozolomide b. Lenalidomide c. High-dose methotrexate	500 mg/m^2 per dose

Chronic lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL)	When the member's disease is CD20-positive	500 mg/m^2 per dose
Hairy Cell Leukemia	When used for **ONE** of the following: 1. In combination with cladribine or pentostatin for relapsed or refractory disease 2. As a single agent if unable to receive purine analog therapy for relapsed or refractory disease 3. In combination with vemurafenib (Zelboraf) to treat disease progression when non-responsive to purine analog therapy (e.g., cladribine or pentostatin)	375 mg/m^2 per dose
Hodgkin Lymphoma (Nodular Lymphocyte-predominant Hodgkin Lymphoma)	When the member's disease is CD20-positive	375 mg/m^2 per dose
Immune Checkpoint Inhibitor-related toxicity	When used for the treatment of checkpoint inhibitor-related encephalitis and **ALL** of the following: 1. Member's encephalitis developed following use of a checkpoint inhibitor (e.g., atezolimumab, avelumab, durvalumab, ipilimumab, nivolumab, pembrolizumab) 2. Member's encephalitis is positive for autoimmune encephalopathy antibody 3. Member had an inadequate response to methylprednisolone or IVIG 4. Viral causes have been ruled out	375 mg/m^2 per dose*
Non-Hodgkin's B-cell Lymphomas (e.g., AIDS-related B-cell lymphoma, Burkitt lymphoma, Diffuse large B-cell lymphoma, Double/Triple Hit Lymphoma, Follicular lymphoma, Gastric MALT lymphoma, Grey Zone lymphoma, High Grade B-cell lymphoma unspecified, Mantle cell lymphoma, Marginal Zone lymphoma, Nodal Marginal zone lymphoma, Non-gastric MALT lymphoma, Primary Cutaneous B-cell Lymphoma Leg type, Primary Mediastinal Large B-cell	When the member's disease is CD20-positive	375 mg/m^2 per dose

lymphoma, Splenic marginal zone lymphoma)		
Post-transplant lymphoproliferative disease (PTLD)	When used for **ONE** of the following: 1. first-line therapy for monomorphic or polymorphic PTLD 2. second-line therapy for partial response, persistent or progressive early lesions 3. second-line therapy for partial response, persistent or progressive monomorphic or polymorphic PTLD 4. maintenance therapy for polymorphic PTLD achieving complete response on first-line therapy 5. member's disease is refractory to a reduction in immunosuppression	375 mg/m^2 per dose
Primary Cutaneous B-cell lymphoma (e.g., Cutaneous Marginal Zone lymphoma or Cutaneous Follicle Center lymphomas)	When disease is classified with **ONE** of the following: 1. Generalized skin involvement (T3) 2. Extracutaneous disease	375 mg/m^2 per dose
Waldenström's macroglobulinemia/Lymphoplasmacytic lymphoma	When used as a single agent or with **ONE** of the following: 1. Bendamustine 2. Bortezomib with or without dexamethasone 3. Carfilzomib and dexamethasone 4. Cladribine 5. Cyclophosphamide and dexamethasone 6. Cyclophosphamide, doxorubicin, vincristine, and prednisone 7. Cyclophosphamide and fludarabine 8. Cyclophosphamide and prednisone 9. Fludarabine 10. Ibrutinib	375 mg/m^2 per dose
Other FDA-approved or NCCN supported diagnosis (not	When **ONE** of the following is met:	Dose does

previously listed above)	1. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert) 2. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation	not exceed the maximum FDA-approved dosing
*Alternative dose: 1000 mg given on day 1 and 15 (given in combination with a tapering dose of corticosteroids) Approval duration: 6 months for all indications except RA (approval duration is 16 weeks).		

2. **Continuation** of rituximab, rituximab-abbs, or rituximab-pvvr **meets the definition of medical necessity** for the indications in Table 1 when **ALL** of the following criteria are met:

a. Member has a history of beneficial response to therapy

b. The member has been previously approved by Florida Blue or another healthplan in the past 2 years, **OR** the member has previously met all indication-specific criteria

c. The dose does not exceed **ANY** of the following based on indication for therapy:

i. Neuromyelitis optica and RRMS: 1000 mg administered on day 1 and 15 every 24 weeks

ii. Rheumatoid arthritis: 1000 mg administered on day 1 and 15 every 16 weeks

iii. Chronic lymphocytic leukemia,Small lymphocytic lymphoma, or Primary CNS Lymphoma: 500 mg/m^2 per dose

iv. CNS cancer, Leptomeningeal Metastases (Intrathecal administration): 25 mg per dose

v. Moderate to severe pemphigus vulgaris if initial dose of 1000mg was given on day 1 and 15: 500 mg administered 12 months after initial dose and every 6 months thereafter**

vi. Granulomatosis with Polyangiitis (GPA or Wegener's granulomatosis), Microscopic Polyangiitis (MPA): 500 mg administered on day 1 and 15 followed by 500 mg every 16 weeks

i. All other indications: 375 mg/m^2 per dose

Approval duration: 1 year

**If disease relapse occurs, a dose of 1000 mg can be administered at least 16 weeks following the previous dose

1. **Initiation** of rituximab hyaluronidase (Rituxan Hycela™) **meets the definition of medical necessity** when administered following an initial single dose of IV rituximab for the indications listed in Table 2 and **ALL** of the indication-specific and maximum-allowable dose criteria are met:

Table 2

Indications and Specific Criteria		
Indication	**Specific Criteria**	**Maximum Allowable Dose**
AIDS-related B-cell Lymphoma	When used as a substitute for rituximab as a single agent or with other systemic therapies and member's disease is CD20-positive	1400 mg per dose
Burkitt Lymphoma	When used as a substitute for rituximab with other systemic therapies and member's disease is CD20-positive	1400 mg per dose
Castleman's Disease (CD)	When used as a substitute for rituximab as a single agent or with other systemic therapies and member has ONE of the following: 1. Multicentric CD 2. Unicentric CD and ONE of the following is met: a. Disease is surgically unresectable b. Member is symptomatic following incomplete/partial resection c. Disease is relapsed or refractory	1400 mg per dose
Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL)	**ONE** of the following is met: 1. When used in combination with fludarabine and cyclophosphamide (FC) 2. When used as a substitute for rituximab as a single agent or with other systemic therapies† and member's disease is CD20-positive	1600 mg per dose
Diffuse Large B-cell Lymphoma (DLBCL)	**ONE** of the following is met: 1. When **BOTH** of the following are met: a. Member has previously untreated diffuse large B-cell lymphoma b. Use is in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-	1400 mg per dose

	based chemotherapy regimens 2. When used as a substitute for rituximab as a single agent or with other systemic therapies† and member's disease is CD20-positive	
Follicular Lymphoma (FL)	**ONE** of the following is met: 1. Use is in combination with first line chemotherapy in previously untreated follicular lymphoma 2. Single agent use for **ONE** of the following: a. Relapsed or refractory, follicular lymphoma b. Maintenance therapy in members achieving a complete or partial response to rituximab in combination with chemotherapy c. Non-progressing (including stable disease), follicular lymphoma after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy 3. When used as a substitute for rituximab as a single agent or with other systemic therapies† and member's disease is CD20-positive	1400 mg per dose
Gastric MALT Lymphoma	When used as a substitute for rituximab as a single agent or with other systemic therapies† and member's disease is CD20-positive	1400 mg per dose
Hairy Cell Leukemia	When used as a substitute for rituximab for **ONE** of the following: 1. In combination with cladribine or pentostatin for relapsed or refractory disease 2. As a single agent if unable to receive purine analog therapy for relapsed or refractory disease 3. In combination with vemurafenib (Zelboraf) to treat disease progression when non-responsive to purine analog therapy (e.g., cladribine or pentostatin)	1400 mg per dose

High-grade B-cell Lymphomas	When used as a substitute for rituximab as a single agent or with other systemic therapies† and member's disease is CD20-positive	1400 mg per dose
Mantle Cell Lymphoma	When used as a substitute for rituximab as a single agent or with other systemic therapies and member's disease is CD20-positive	1400 mg per dose
Nodal Marginal Zone Lymphoma	When used as a substitute for rituximab as a single agent or with other systemic therapies† and member's disease is CD20-positive	1400 mg per dose
Nongastric MALT Lymphoma	When used as a substitute for rituximab as a single agent or with other systemic therapies† and member's disease is CD20-positive	1400 mg per dose
Post-transplant Lymphoproliferative Disorder (PTLD)	When used as a substitute for rituximab as a single agent or with other systemic therapies for ONE of the following: 1. first-line therapy for monomorphic or polymorphic PTLD 2. second-line therapy for partial response, persistent or progressive early lesions 3. second-line therapy for partial response, persistent or progressive monomorphic or polymorphic PTLD 4. maintenance therapy for polymorphic PTLD achieving complete response on first-line therapy	1400 mg per dose
Primary Cutaneous B-cell lymphoma (e.g., Cutaneous Marginal Zone lymphoma or Cutaneous Follicle Center lymphomas)	When used as a substitute for rituximab as a single agent or with other systemic therapies† and disease is classified with **ONE** of the following: 1. Generalized skin involvement (T3) 2. Extracutaneous disease	1400 mg per dose

Splenic Marginal Zone Lymphoma	When used as a substitute for rituximab as a single agent or with other systemic therapies† and member's disease is CD20-positive	1400 mg per dose
Other FDA-approved or NCCN supported diagnosis (not previously listed above)	When **ONE** of the following is met: 1. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert) 2. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation	Dose does not exceed the maximum FDA-approved dosing
†Excludes use in combination with ibritumomab tiuxetan (Zevalin) Approval duration: 6 months		

2. **Continuation** of rituximab hyaluronidase (Rituxan Hycela™) meets **the definition of medical necessity** for the indications in Table 2 when **ALL** of the following criteria are met:

a. Member has a history of beneficial response to therapy
b. The member has been previously approved by Florida Blue or another healthplan in the past 2 years, **OR** the member has previously met all indication-specific criteria
c. The dose does not exceed indication specific dosing in Table 2.

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

Rituximab

Rituximab is FDA-approved for treatment of non-Hodgkin's Lymphoma (NHL), chronic lymphocytic leukemia (CLL), rheumatoid arthritis (RA), granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis), microscopic polyangiitis (MPA) and moderate to severe pemphigus vulgaris (PV). Rituximab should be used in combination with methotrexate in individuals with moderately to severely active RA who have had an inadequate response to one or more TNF antagonist therapies. The recommended dosage regimens for FDA-approved indications are listed in table 3. See prescribing information for dosing information of biosimilar products rituximab-abbs and rituximab-pvvr.

Table 3

FDA-approved indications and dosage regimens	
Indication	**Dose**
NHL†	375 mg/m^2
CLL	375 mg/m^2 prior to initiation of FC, then 500 mg/m^2 on day1 of cycles 2-6
RA	Two-1000 mg infusions separated by 2 weeks‡; subsequent infusions should administered every 24 weeks or based on clinical evaluation. Do not administer sooner than every 16 weeks
GPA/MPA	375 mg/m^2 once weekly for 4 weeks±. Follow up treatment for patients who achieve disease control: Two-500 mg infusions separated by 2 weeks‡ followed by 500 mg every 6 months therafter based on clinical evaluation; subsequent infusions should administered every 24 weeks or based on clinical evaluation. Do not administer sooner than every 16 weeks.
PV	Two-1000 mg infusions separated by 2 weeks‡ in combination with a tapering course of glucocorticoids; then a 500 mg infusion at month 12 and every 6 months thereafter or based on clinical evaluation. Dose upon relapse is a 1000 mg infusion with consideration to resume or increase the glucocorticoid dose based on clinical evaluation. Do not administer sooner than every 16 weeks after the previous infusion.

† Schedule is based on type of NHL, dose is 250 mg/m2 if used as a component of Zevalin® for NHL

‡ Administer methylprednisolone 100 mg IV or its equivalent 30 minutes prior to each infusion

± Administration of methylprednisolone 1000 mg IV daily for 1-3 days followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day and tapered per clinical need) are recommended to treat severe vasculitis symptoms.

NHL, non-Hodgkin's Lymphoma; CLL, chronic lymphocytic leukemia; FC, fludarabine and cyclophosphamide; RA, rheumatoid arthritis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; PV, pemphigus vulgaris.

Rituximab should be administered as an intravenous (IV) infusion and should not be administered as an IV push or IV bolus. Premedication should be administered prior to each infusion (e.g., acetaminophen, antihistamine). Initially, rituximab should be administered at a rate of 50 mg/hr; in the absence of infusion toxicity, the rate can be increased by 50 mg/hr increments at 30-minute intervals to a maximum of 400 mg/hr.

Rituximab; Hyaluronidase

FDA-approved: rituximab; hyaluronidase is indicated for treatment of Follicular Lymphoma (FL), Diffuse Large B-cell Lymphoma (DLBCL), and Chronic Lymphocytic Leukemia (CLL), Rituximab;hyaluronidase is not indicated for the treatment of non-malignant conditions.

All patients must receive at least one full dose of a rituximab product by intravenous infusion before receiving rituximab;hyaluronidase by subcutaneous injection. Rituximab;hyaluronidase should be administered by a healthcare professional with medical support to manage severe reactions. Premedicate with acetaminophen and antihistamine before each dose and consider premedication with glucocorticoids.

FL/DLBCL: Administer 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human) subcutaneously. See prescribing information for recommended schedule and use of concomitant medications.

CLL: Administer 1,600 mg/26,800 Units (1,600 mg rituximab and 26,800 Units hyaluronidase human) subcutaneously. See prescribing information for recommended schedule and use of concomitant medications.

Administer specified volume into subcutaneous tissue of abdomen and observe 15 minutes following administration. Do not administer other subcutaneous medications at the same site of administration.

11.7 mL from 1,400 mg/23,400 Units vial over approximately 5 minutes.

13.4 mL from 1,600 mg/26,800 Units vial over approximately 7 minutes.

Drug Availability:

Rituximab, rituximab-abbs, and rituximab-pvvr are each supplied as a 100 mg/10 ml and 500 mg/50 mL solution in a single-use vial.

Rituximab;hyaluronidase is supplied as 1,400 mg/23,400 units per 11.7 mL and 1,600 mg/26,800 units per 13.4 mL

PRECAUTIONS:

Boxed Warning

- Fatal infusion reactions within 24 hours of rituximab infusion can occur; approximately 80% of fatal reactions occurred with first infusion. Monitor members and discontinue rituximab infusion for severe reactions
- Severe mucocutaneous reactions, some with fatal outcomes can occur.
- Hepatitis B reactivation with fulminant hepatitis, hepatic failure and death; screen patients for HBV prior to initiation and monitor patients during and several months after therapy. Discontinue rituximab if reactivation occurs
- Progressive multifocal leukoencephalopathy (PML) resulting in death can occur in persons receiving rituximab. Monitor neurologic function and discontinue rituximab if PML occurs.

Warnings

- Tumor lysis syndrome (TLS): acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia or hyperphosphatemia, requiring dialysis with instances of fatal outcome can occur in the setting of TLS following treatment of NHL persons with rituximab. Administer aggressive IV hydration, anti-hyperuricemic agents, and monitor renal function

- Infections – serious, fatal infections can occur. Withhold rituximab and institute appropriate anti-infective therapy
- Cardiac arrhythmias and angina can occur and can be life threatening. Monitor individuals with these conditions closely
- Renal toxicity – severe, fatal renal toxicity can occur. Monitor for signs and symptoms of renal failure.
- Bowel obstruction and perforation – some cases have lead to death, evaluate complaints of abdominal pain
- Do not administer live virus vaccines prior to or during rituximab
- Monitor CBC and platelet counts prior to therapy and at regular intervals for severe cytopenias
- Hypersensitivity reactions and local cutaneous reactions may occur during administration or more than 24 hours after subcutaneous administration. Premedicate and Interrupt if severe infusion reaction occurs.
- Embryo-fetal toxicity- may cause harm to a developing fetus and effective contraception should be utilized up to 12 months following administration.

BILLING/CODING INFORMATION:

HCPCS Coding for rituximab:

J9312	Injection, rituximab, 10 mg
Q5115	Injection, rituximab-abbs, biosimilar, (Truxima), 10 mg

HCPCS Coding for rituximab; hyaluronidase:

J9311	Injection, rituximab 10 mg and hyaluronidase

ICD-10 Diagnosis Codes That Support Medical Necessity for rituximab (J9312, Q5115):

B10.89	Other human herpes virus infection
B20	Human immunodeficiency virus [HIV] disease
C79.32	Secondary malignant neoplasm of cerebral meninges
C79.40	Secondary malignant neoplasm of unspecified part of nervous system
C79.49	Secondary malignant neoplasm of other parts of nervous system
C81.00 – C81.09	Nodular lymphocyte predominant Hodgkin lymphoma
C81.40 – C81.49	Lymphocyte-rich Hodgkin lymphoma
C82.00 – C82.69	Follicular lymphoma of various sites
C82.80 – C82.99	Other specified types of follicular lymphoma and unspecified follicular lymphoma
C83.00 – C83.99	Small cell B-cell lymphoma, Mantle cell lymphoma, diffuse large B-cell lymphoma, lymphoblastic (diffuse) lymphoma, Burkitt lymphoma and other non-follicular lymphoma
C84.90 – C84.99	Cutaneous T-cell lymphoma various sites
C84.A0 – C84.A9	Other mature T/NK-cell lymphomas, various sites
C84.Z0 – C84.Z9	Mature T/NK-cell lymphomas, unspecified various sites
C85.10 – C85.99	Other specified and unspecified types of non-Hodgkin lymphoma, various sites
C86.0 – C86.66	Other specified types of T/NK-cell lymphoma
C88.0	Waldenstrom macroglobulinemia

C88.4	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (Malt- lymphoma)
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.01	Acute lymphoblastic leukemia, in remission
C91.02	Acute lymphoblastic leukemia, in relapse
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
C91.40 – C91.42	Hairy cell leukemia
C91.90	Lymphoid leukemia, unspecified not having achieved remission
D36.0	Benign neoplasm of lymph nodes
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)
D47.Z2	Castleman disease
D59.0	Drug-induced autoimmune hemolytic anemia
D59.1	Other autoimmune hemolytic anemias
D66	Hereditary factor VIII deficiency
D67	Hereditary factor IX deficiency
D68.1	Hereditary factor XI deficiency
D68.311	Acquired hemophilia
D69.3 – D69.49	Immune thrombocytopenic purpura, Evans syndrome, congenital and hereditary thrombocytopenia purpura and other primary thrombocytopenia
D69.6	Thrombocytopenia, unspecified
D89.1	Cryoglobulinemia
D89.811 – D89.813	Chronic, graft-versus-host disease
G04.81	Other encephalitis and encephalomyelitis (checkpoint inhibitor toxicity)
G35	Multiple sclerosis
G36.0	Neuromyelitis optica [Devic]
G70.00 – G70.01	Myasthenia gravis
L10.0 – L10.9	Pemphigus vulgaris and other pemphigus types
L12.0 – L12.9	Pemphigoid of various types
L13.8	Other specified bullous disorders
L13.9	Bullous disorder, unspecified
L14	Bullous disorders in diseases classified elsewhere
L51.2	Toxic epidermal necrolysis [Lyell]
M05.00 – M05.09	Felty's syndrome, various sites
M05.10 – M05.19	Rheumatoid lung disease with rheumatoid arthritis of various sites
M05.20 – M05.29	Rheumatoid vasculitis with rheumatoid arthritis of various sites
M05.30 – M05.39	Rheumatoid heart disease with rheumatoid arthritis of various sites
M05.40 – M05.49	Rheumatoid myopathy with rheumatoid arthritis of various sites
M05.50 – M05.59	Rheumatoid polyneuropathy with rheumatoid arthritis of various sites
M05.60 – M05.69	Rheumatoid arthritis with involvement of other organs and systems, various sites
M05.70 – M05.79	Rheumatoid arthritis with rheumatoid factor without involvement of other organs and systems, various sites
M05.80 – M05.89	Other rheumatoid arthritis with rheumatoid factor of various sites
M05.9	Rheumatoid arthritis with rheumatoid factor, unspecified
M06.00 – M06.09	Rheumatoid arthritis without rheumatoid factor, various sites
M06.1	Adult-onset Still's disease
M06.4	Inflammatory polyarthropathy

M06.80 – M06.89	Other specified rheumatoid arthritis, various sites
M06.9	Rheumatoid arthritis, unspecified
M30.0	Polyarteritis nodosa
M30.1	Polyarteritis with lung involvement [Churg-Strauss]
M31.0	Hypersensitivity angiitis
M31.1	Thrombotic microangiopathy
M31.30	Wegener's granulomatosis without renal involvement
M31.31	Wegener’s granulomatosis with renal involvement
M31.7	Microscopic polyangiitis
M32.0 – M32.9	Systemic lupus erythematosus, organ or system involvement unspecified
M35.00 – M35.09	Sicca syndrome, various areas of involvement
N04.0 – N04.9	Nephrotic syndrome
N05.0 – N05.9	Unspecified nephritic syndrome
Q81.0 – Q81.9	Epidermolysis bullosa, unspecified
Q82.9	Congenital malformation of skin, unspecified
Q82.8	Other specified congenital malformations of skin
R59.0 – R59.9	Enlarged lymph nodes, unspecified
T86.00 – T86.02	Complications of bone marrow transplant
T86.09	Other complications of bone marrow transplant
T86.10 – T86.12	Complications of kidney transplant
T86.19	Other complications of kidney transplant
T86.20 – T86.22	Complications of heart transplant
T86.298	Other complications of heart transplant
T86.30 – T86.32	Complications of heart-lung transplant
T86.39	Other complications of heart-lung transplant
T86.40 – T86.42	Complications of liver transplant
T86.49	Other complications of liver transplant
T86.5	Complications of stem cell transplant
T86.810 – T86.811	Complications of lung transplant
T86.818 – T86.819	Other or Unspecified complications of lung transplant
T86.820 – T86.821	Complications of skin graft (allograft) (autograft)
T86.828 – T86.829	Other or unspecified complications of skin graft (allograft) (autograft)
T86.830 – T86.831	Complications of bone graft
T86.838 – T86.839	Other or unspecified complication of bone graft
T86.840 – T86.841	Complications of corneal transplant
T86.848 – T86.849	Other or unspecified complication of corneal transplant
T86.850 – T86.851	Complication of intestine transplant
T86.858 – T86.859	Other or Unspecified complications of intestine transplant
T86.890 – T86.891	Complications of other transplanted tissue
T86.898 – T86.899	Other or Unspecified complication of other transplanted tissue
T86.90 – T86.92	Complication of unspecified transplanted organ and tissue
T86.99	Other complications of unspecified transplanted organ and tissue
Z48.22	Encounter for aftercare following kidney transplant
Z94.0	Kidney transplant status

ICD-10 Diagnosis Codes That Support Medical Necessity for rituximab;hyaluronidase (J9311):

B20	Human immunodeficiency virus [HIV] disease
C82.00 – 82.99	Follicular lymphoma of various sites
C83.00 – C83.09	Small cell B-cell lymphoma
C83.10 – C83.19	Mantle cell lymphoma
C83.30 – C83.39	Diffuse large B-cell lymphoma
C83.70 – C83.89	Burkitt lymphoma
C85.20 – C85.29	Mediastinal (thymic) large B-cell lymphoma
C85.80 – C85.89	Other specified types of non-Hodgkin lymphoma
C88.4	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma]
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
C91.40	Hairy cell leukemia, not having achieved remission
C91.42	Hairy cell leukemia in relapse
D36.0	Benign neoplasm of lymph nodes
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)
D47.Z2	Castleman disease
R59.0 – R59.9	Enlarged lymph nodes

REIMBURSEMENT INFORMATION:

Please refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: No National Coverage Determination (NCD) was found at the time of the last guideline revised date. The following Local Coverage Determination (LCD) was reviewed on the last guideline revised date: Rituximab, (L33746) located at fcso.com.

DEFINITIONS:

RA: Rheumatoid Arthritis.

TNF: tumor necrosis factor.

HyperCVAD: hyper-fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone

RELATED GUIDELINES:

Abatacept (Orencia®), 09-J0000-67
Adalimumab (Humira®), 09-J0000-46
Anakinra (Kineret®), 09-J0000-45
Certolizumab Pegol (Cimzia®), 09-J0000-77

Etanercept (Enbrel®), 09-J0000-38
Golimumab (Simponi™), 09-J1000-11
Infliximab (Remicade®), 09-J0000-39

OTHER:

None applicable.

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue BCBSF Pharmacy Policy Committee on 09/11/19.

GUIDELINE UPDATE INFORMATION:

08/15/06	New Medical Coverage Guideline.
10/15/06	Revised: added highlighted note stating that this MCG only addresses use in rheumatoid arthritis and does not address rituximab use in oncological applications, revised descriptor of HCPCS code and removed Medicare Advantage from program exceptions.
06/15/07	Review and revision; consisting of reformatting guideline, adding Remicade® in parentheses in criteria after failure of TNF antagonists, added ICD-9 codes in order to be compliant with FCSO LCD, updated related guidelines and updated references.
05/15/08	Review and revision; consisting of adding a black box warning under “PRECAUTIONS” and updating references.
11/15/08	Revision; consisting of updating the boxed warning under the Precautions section and removing the experimental and investigational statement from the Position Statement and adding “Re-treatment is not supported in the literature sooner than 6 months after initial treatment AND is investigational”.
01/01/09	Annual HCPCS coding update: revised descriptor for code J9310; deleted 90765 and 90766; added 96365 and 96366.
05/15/09	Revision; consisting of changing name of guideline, adding oncologic indications, maximum doses and updating references.
09/15/09	Review and revision; consisting of updating references.
10/15/09	Revision; consisting of clarifying dosage and update coding.
08/01/10	Revision; consisting of updating coding.
10/15/10	Revision; consisting of updating coding.
02/01/11	Review and revision; consisting of adding new indication, removing an indication, updating approved dosages, and references and coding.
05/15/11	Revision to guideline; consisting of updating coding and adding alternate dosing regimen.
07/15/11	Revision to guideline; consisting of add 2 new indications.
01/15/11	Review and revision to guideline; consisting of updating references and coding
07/15/12	Review and revision to guideline; consisting of updating position statement, coding, exceptions and references
12/15/12	Revision to guideline; consisting of updating coding.
04/15/13	Revision to guideline; consisting of updating position statement and coding.
09/15/13	Review and revision to guideline; consisting of revising and reformatting position statement, revising description section, dosage/administration section, precautions section, updated program exceptions and references.
09/15/14	Review and revision to guideline; consisting of reformatting the position statement; updating references and coding.
04/15/15	Revision to guidelines; updating coding.
09/15/15	Review and revision to guideline; consisting of revising position statement, dosing/warnings/precautions section, updated coding and references.
10/01/15	Revision consisting of update to Program Exceptions section.
11/01/15	Revision: ICD-9 Codes deleted.
05/15/16	Revision to codes.
06/15/16	Revision to guideline; consisting of updating position statement and references.
10/01/16	Update to ICD-10 codes.
09/15/17	Review and revision to guideline; consisting of updating the position statement; dosing, coding, and references.
10/15/17	Revision to guideline; consisting of updating position statement and references.

03/15/18	Revision to guideline; consisting of updating position statement, coding and references.
04/01/18	Addition of HCPCS code C9467 and deletion of C9399.
07/15/18	Review and revision to guideline; consisting of updating the position statement, coding and references.
08/15/18	Revision to guideline; consisting of updating the position statement and references.
01/01/19	Revision: HCPCS code updates. Added J9311 and J9312, and removed C9467, J9310, and J9999.
10/15/19	Review and revision to guideline; consisting of updating the position statement, description, coding and references.