Rituximab Medical Drug Criteria Program Summary

For BCBS KS, the following preferred agents are **not** subject to prior authorization: Ruxience, Truxima

POLICY REVIEW CYCLE

Effective Date 06-16-2025

Date of Origin

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#

Riabni®
 	
(rituximab-arrx)
 	
Injection for intravenous use
	• 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 a rituximab product in combination with chemotherapy, as 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 sulfate, 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 previously untreated and previously treated CD20-positive chronic lymphocytic leukemia (CLL) in combination with fludarabine and cyclophosphamide (FC)
	• Treatment of adult patients with moderately-to severely-active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies
	• Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids
			25

Rituxan®
 	
(rituximab)
 	
Injection for intravenous use
	• 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 a rituximab product in combination with chemotherapy, as single-agent maintenance therapy
			1

Agent(s)	FDA Indication(s)	Notes	Ref#
	○ Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine sulfate, 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 • Pediatric patients aged 6 months and older with previously untreated, advanced stage, CD20-positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL), or mature B-cell acute leukemia (B-AL) in combination with chemotherapy • Adult patients with chronic lymphocytic leukemia (CLL) ○ Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC) • Treatment of adult patients with moderately-to severely-active rheumatoid arthritis who have had 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 • Moderate to severe pemphigus vulgaris (PV) in adult patients		
Rituxan® Hycela (rituximab and hyaluronidase human) Injection for subcutaneous use	Treatment of adult patients with: • Follicular Lymphoma (FL) ○ Relapsed or refractory, follicular lymphoma as a single agent ○ 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 a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy • Diffuse Large B-cell Lymphoma (SLBCL) ○ Previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin,		2

Agent(s)	FDA Indication(s)	Notes	Ref#
	vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens • Previously untreated and previously treated chronic lymphocytic leukemia (CLL) in combination with fludarabine and cyclophosphamide (FC) Limitations of use: • Initiate treatment with Rituxan Hycela only after patients have received at least one full dose of a rituximab product by intravenous infusion • Rituxan Hycela is not indicated for the treatment of non-malignant conditions		
Ruxience® (rituximab-pvvr) Injection for intravenous use	• Adult patients with Non-Hodgkin's Lymphoma (NHL) o Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent o 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 o 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 o 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) o Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC) • Treatment of adult patients with moderately-to severely-active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies • Granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis) and microscopic polyangiitis (MPA) in adult patients in combination with glucocorticoids		7
Truxima® (rituximab-abbs)	• Adult patients with Non-Hodgkin's Lymphoma (NHL) o Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma (NHL) as a single agent		6

Agent(s)	FDA Indication(s)	Notes	Ref#
Injection for intravenous use	○ 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 ○ 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 and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC) • Treatment of adult patients with moderately-to severely-active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies • Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids		

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

ONCOLOGY - Non-Hodgkin lymphoma (NHL)	Non-Hodgkin lymphoma (NHL) consists of a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes, or natural killer (NK) cells (NK/T-cell lymphomas are very rare). Types of NHL include diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), and peripheral T-cell lymphoma not otherwise specified (PTCL-NOS). Overall, with current treatment options patients with NHL have an overall survival rate at 5 years of approximately 50-60% with 30% of patients with aggressive disease being able to be cured.(4)
ONCOLOGY-Diffuse Large B-Cell Non-Hodgkin Lymphoma (NHL)	B-cell lymphomas make up about 85% of NHL lymphomas in the United States. B lymphocytes are responsible for generating proteins (antibodies) that attach to bacteria and viruses and mark them for elimination by the immune system. Diffuse large B-cell is the most common type of NHL in the U.S, and it accounts for 1 out of every 3 cases. Treatment for B-cell NHL includes radiation therapy, immunotherapy with rituximab, systemic chemotherapy, or a combination of these therapies.(3)
ONCOLOGY- Follicular Lymphoma (FL)	Follicular lymphoma (FL) comprises 20% of all NHL and as many as 70% of the indolent lymphomas reported in American and European clinical trials. Most patients with FL are age 50 years and older and present with widespread disease at diagnosis. Nodal involvement is most common and is often accompanied by splenic and bone marrow disease. Rearrangement of the BCL2 gene is present in more than 90% of patients with FL; overexpression of the BCL2 protein is associated with the inability to eradicate the lymphoma by inhibiting apoptosis.(3)

ONCOLOGY-Chronic Lymphocytic Lymphoma (CLL)	Chronic lymphocytic leukemia (CLL) is one of the chronic lymphoproliferative disorders (lymphoid neoplasms). It is characterized by a progressive accumulation of functionally incompetent lymphocytes, which are usually monoclonal in origin. The National Cancer Institute estimates that in 2018 there will be 20,940 new cases of CLL and 4,510 deaths from CLL in the United States. There is no single agreed upon standard treatment regimen for symptomatic chronic CLL. Experts in the field use different treatment approaches which include purine analogs, alkylating agents, monoclonal antibodies, tyrosine kinase inhibitors or combinations of these therapies.(5)
ONCOLOGY-Efficacy	Rituximab is a monoclonal antibody directed against CD20 antigen. It binds to the antigen CD20 on pre-B and mature B lymphocytes. Upon binding to CD20, rituximab mediates B-cell lysis. The FDA approval of rituximab for the treatment of NHL was based on several trials with primary endpoints of overall response rate and progression free survival (PFS). Study results showed significance for these primary endpoints. See labeling for study details.(1) Rituxan Hycela is a combination of rituximab and hyaluronidase human. Recombinant human hyaluronidase is an endoglycosidase use to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. The effects of hyaluronidase human are reversible, and permeability of the subcutaneous tissue is restored within 24 to 48 hours.(2)
ONCOLOGY-Efficacy: B-Cell Non-Hodgkin Lymphoma (NHL)	The safety and effectiveness of Rituxan were evaluated in three randomized, active-controlled, open-label, multicenter studies with a collective enrollment of 1854 patients [Listed in prescribing information as Study 7 (632 patients), Study 8 (399 patients), and Study 9 (823 patients)]. Patients with previously untreated diffuse large B-cell NHL received Rituxan in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens. The main outcome measure of study 7 was PFS. PFS was defined as the time from randomization to the first progression, relapse, or death. Patients had a PFS of 3.1 years in the R-CHOP group vs 1.6 years in the CHOP group. The main outcome of study 8 was event-free survival (EFS), defined as the time from randomization to relapse, progression, change in therapy, or death from any cause. Patients had an EFS of 2.9 years in the R-CHOP group vs 1.1 years in the CHOP group. The main outcome in study 9 was time to treatment failure (TTF), defined as time from randomization to the earliest of progressive disease, failure to achieve a complete response, relapse, or death. The study concluded that the TTF was not reliably estimable in both the R-Chemo and Chemo groups but did conclude that the R-Chemo group had an overall survival at 2 years of 95% vs only 86% in the Chemo group.(1) The biosimilars showed similar results to Rituxan with their conducted studies.(6,7,25) Rituxan Hycela was evaluated in previously untreated adult patients outside of the United States with CD20-positive diffuse large B-cell lymphoma or CD20-positive follicular non-Hodgkin’s lymphoma. 620 patients were randomized to receive a standard chemotherapy regimen and either a rituximab product given intravenously on cycle 1 followed by Rituxan Hycela 1,400 mg/23,400 Units for cycles 2-4 or a rituximab product given by intravenous infusion for cycles 1-4. After the 4th cycle, patients were crossed over to the alternative route of administration for the remaining 4 cycles. After cycle 8 the subcutaneous route of administration was preferred by 77% of the patients with the most common reason being less time spent in the clinic. 11% of the patients said they preferred the intravenous route of administration with the most common reason given that it felt more comfortable during administration. 7.7% of patients had no preference and 4.7% did not complete the preference questionnaire.(2)
ONCOLOGY-Efficacy: Follicular Lymphoma (FL)	Approval for the use of Rituxan in the treatment of follicular NHL was evaluated in previously untreated patients who were randomized to either eight 3-week cycles of chemotherapy alone or in combination with rituximab. PFS was the primary efficacy outcome. Median PFS was 2.4 years in the rituximab + chemotherapy group compared to 1.4 years in the chemotherapy group alone (p less than 0.0001). Monotherapy maintenance was evaluated in an open label trial in patients who achieved a response to rituximab in combination with chemotherapy. Patients were randomized to either rituximab as monotherapy or observation. The main outcome measure was PFS. PFS

	was longer in patients randomized to rituximab as monotherapy maintenance.(1) The biosimilars showed similar results to Rituxan in their conducted studies.(6,7,25) Rituxan Hycela for follicular lymphoma was evaluated in a randomized, two-stage, open-label, multicenter study that enrolled a total of 410 patients with previously untreated, CD20-positive follicular lymphoma of Grade 1, 2, or 3a requiring therapy. The study design was identical in stages 1 and 2. 205 patients were randomized in each arm. In one arm, the patients received a rituximab product by intravenous infusion at a dose of 375 mg/m^2 every 3 weeks for 8 cycles and the other arm the patients received 1 cycle of a rituximab product by intravenous infusion followed by 7 cycles of Rituxan Hycela 1,400mg/23,400 Units every 3 weeks. All patients also received either 6-8 cycles of CHOP [cyclophosphamide + doxorubicin hydrochloride (hydroxydaunorubicin) + vincristine sulfate (Oncovin) + prednisone] or 8 cycles of CVP (cyclophosphamide + vincristine sulfate+ prednisone) along with the study drug. The patients underwent interim staging after 4 cycles and those patients that received Rituxan + CHOP or Rituxan Hycela + CHOP and achieved a complete response, unconfirmed complete response, partial response, or stable disease could receive either 4 more cycles of rituximab product/Rituxan Hycela + CHOP or 2 cycles of rituximab product/Rituxan Hycela + CHOP followed by 2 cycles of monotherapy with rituximab product or Rituxan Hycela. Patients with at least a partial response after combination treatment with chemotherapy continued with singe agent maintenance treatment with rituximab product or Rituxan Hycela every 8 weeks for 24 months. The pharmacokinetic results in Stage 1 of the study demonstrated that Rituxan Hycela was non-inferior compared with rituximab. The efficacy results for Rituxan Hycela were comparable with rituximab.(2)
ONCOLOGY-Efficacy: Chronic Lymphocytic Lymphoma (CLL)	Rituxan is labeled for the treatment of CLL in combination with fludarabine and cyclophosphamide in patients with CD20-positive disease. The safety and efficacy were evaluated in 2 randomized, open-label studies comparing fludarabine and cyclophosphamide (FC) alone to rituximab in combination with FC in both treatment naïve and treatment experienced patients. The primary outcome measure of both studies was PFS. The median PFS in previously untreated patients was 39.8 months in the RFC group compared to 31.5 months. Median PFS in previously treated patients in the RFC group was 26.7 months versus 21.7 months in the FC alone group.(1) The biosimilars showed similar results to Rituxan in their respective studies.(6,7,25) Rituxan Hycela for CLL was evaluated in a randomized, two-part, open-label, multi-center study that enrolled a total of 176 patients with previously untreated CLL. 88 patients were randomized in each arm. In one arm, the patients received a rituximab product by intravenous infusion at a dose of 375 mg/m^2 in cycle 1, followed by up to 5 cycles of rituximab 500 mg/m^2. In the second arm, the patients received a rituximab product by intravenous infusion at a dose of 375 mg/m^2 in cycle 1, followed by Rituxan Hycela 1,600 mg/26,800 Units for cycles 2 through 6. Both arms used the study drug alone with fludarabine and cyclophosphamide chemotherapy. The main outcome measure was the non-inferiority of the pharmacokinetic (PK) profile of Rituxan Hycela compared to rituximab. The PK profile results demonstrated that Rituxan Hycela was non-inferior compared with rituximab in patients receiving combination chemotherapy. An additional outcome measure in part 2 was investigator-assessed response rates. Overall response rate in the Rituxan Hycela arm was 85% (95% CI) and 81% (95% CI) in the rituximab arm. Overall the response rate was comparable in the 2 arms.(2)
ONCOLOGY-Safety	Riabni (rituximab-arrx), Rituxan (rituximab), Ruxience (rituximab-pvvr), Truxima (rituximab-abbs) contain boxed warnings for serious, sometimes fatal infusion reactions. Approximately 80% of fatalities due to these infusion reactions are associated with the first infusion. Additional boxed warnings include hepatitis B virus (HBV) reactivation (some cases resulting in fulminant hepatitis, hepatic failure, and death), severe (including fatal) mucocutaneous reactions, and progressive multifocal leukoencephalopathy (PML) resulting in death.(1,6,7,25) Rituxan Hycela contains boxed warnings for severe mucocutaneous reactions (some with fatal outcomes), hepatitis B virus reactivation (some cases resulting in fulminant hepatitis, hepatic failure, and death) and PML resulting in death.(2) Monitor patients for tumor lysis syndrome, PML, hepatitis B reactivation, infections, cardiac arrhythmias and angina, bowel obstruction and perforation.(1,2,6,7,25)

ONCOLOGY-Compendia Supported Indications	For the purposes of the oncology criteria, indications deemed appropriate are those that are supported by NCCN Drugs & Biologics compendia with a category 1 or 2A recommendation.

NON-ONCOLOGY-Rheumatoid Arthritis (RA)	Rheumatoid arthritis (RA) is the most common inflammatory autoimmune arthritis in adults. The main goal of therapy is to achieve remission, but additional goals include decrease inflammation, relieve symptoms, prevent joint and organ damage, improve physical function/overall well-being, and reduce long term complications.(15,32) The choice of therapy depends on several factors, including the severity of disease activity when therapy is initiated and the response of the patient to prior therapeutic interventions.(32)
	
	American College of Rheumatology (ACR) guidelines list the following guiding principles in the treatment of RA:(32)
	
	• RA requires early evaluation, diagnosis, and management
	• Treatment decisions should follow a shared decision-making process
	• Treatment decisions should be reevaluated within a minimum of 3 months based on efficacy and tolerability of the DMARD(s) chosen
	• Recommendations are limited to DMARDs approved by the US FDA for treatment of RA:
	  ○ csDMARDs: hydroxychloroquine, sulfasalazine, methotrexate (MTX), leflunomide
	  ○ bDMARDs: TNF inhibitors (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), T cell costimulatory inhibitor (abatacept), IL-6 receptor inhibitors (tocilizumab, sarilumab), anti-CD20 antibody (rituximab)
	  ○ tsDMARDs: JAK inhibitors (tofacitinib, baricitinib, upadacitinib)
	• Triple therapy refers to hydroxychloroquine, sulfasalazine, and either methotrexate or leflunomide
	• Biosimilars are considered equivalent to FDA-approved originator bDMARDs
	• Recommendations referring to bDMARDs exclude rituximab unless patients have had an inadequate response to TNF inhibitors (in order to be consistent with FDA approval) or have a history of lymphoproliferative disorder for which rituximab is an approved therapy
	• Treat-to-target refers to a systematic approach involving frequent monitoring of disease activity using validated instruments and modifications of treatment to minimize disease activity with the goal of reaching a predefined target (low disease activity or remission)
	
	ACR guidelines are broken down by previous treatment and disease activity:(32)
	
	• DMARD-naïve patients with moderate-to-high disease activity initial treatment:
	  ○ MTX monotherapy is strongly recommended over hydroxychloroquine, sulfasalazine, bDMARDs monotherapy, tsDMARD monotherapy, or combination of MTX plus a non-TNF bDMARD or tsDMARD
	  ○ MTX monotherapy is conditionally recommended over leflunomide, dual or triple csDMARD therapy, or combination MTX plus a TNF inhibitor
	• DMARD-naïve patients with low disease activity initial treatment:
	  ○ Hydroxychloroquine is conditionally recommended over other csDMARDs
	  ○ Sulfasalazine is conditionally recommended over MTX
	  ○ MTX is conditionally recommended over leflunomide
	• Initial therapy in csDMARD-treated patients, but MTX naïve, with moderate-to high disease activity:
	  ○ MTX monotherapy is conditionally recommended over combination MTX and a bDMARD or tsDMARD
	• Treatment Modifications in patients treated with DMARDs who are not at target:

	○ Addition of a bDMARD or tsDMARD is conditionally recommended over triple therapy for patients taking maximally tolerated doses of MTX who are not at target ○ Switching to a bDMARD or tsDMARD of a different class is conditionally recommended over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target Early use of DMARD, particularly MTX, is recommended as soon as possible following diagnosis of RA. Dosing of MTX for RA is once weekly dosing with starting doses at 7.5 mg or 15 mg once weekly.(16-18) MTX dose is increased as tolerated and as needed to control symptoms and signs of RA disease. The usual target dose is at least 15 mg weekly and the usual maximum dose is 25 mg weekly.(17-18) ACR defines optimal dosing for RA treatments as 1) dosing to achieve a therapeutic target derived from mutual patient-clinician consideration of patient priorities and 2) given for at least 3 months before therapy escalation or switching. For patients who are unable to take MTX, hydroxychloroquine, sulfasalazine, or leflunomide are other DMARD options. In patients resistant to initial MTX treatment, combination DMARD (e.g., MTX plus sulfasalazine or hydroxychloroquine or a TNF-inhibitor) is recommended.(32) For patients who are resistant to MTX after 3 months of treatment at optimal doses (usually 25 mg per week), it is recommended to either use DMARD triple therapy with MTX plus sulfasalazine and hydroxychloroquine or combination of MTX with TNF inhibitor. Triple therapy regimen has been found to be of similar clinical efficacy to MTX with biologics in several randomized trials, including in patients with high level of disease activity or with adverse prognostic features. The use of triple therapy has been shown to be highly cost-effective compared with combining a biologic with MTX, providing comparable or near comparable clinical benefit. The use of biologic with MTX combination is preferred when patients have high disease activity and clinical benefit from a more rapid response is needed and when patients who do not achieve satisfactory response within 3 months with non-biologic triple therapy following an inadequate response to MTX therapy.(18,32)
NON-ONCOLOGY-Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis	Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is a rare blood vessel disorder. Common symptoms for GPA include runny nose/nasal congestion, frequent nose bleeds, sinus pain, shortness of breath, and cough. Other early symptoms include fever, weight loss, fatigue, eye problems (vision and/or redness), night sweats, and numbness in fingers, toes, or limbs. Organ failure can be a result of ongoing inflammation, and without treatment, GPA can worsen rapidly, leading to life-threatening liver or kidney failure. Therapy for GPA has two main components: induction of remission with initial immunosuppressive therapy and maintenance of remission with immunosuppressive therapy for variable period to prevent relapse.(26) The American College of Rheumatology (ACR) guidelines recommend the following for initial induction therapy and maintenance of remission for GPA:(28) • Induction: ○ Non-severe disease: ▪ Conditional recommendation of initiating treatment with methotrexate with or without glucocorticoids over cyclophosphamide or rituximab ▪ Conditional recommendation of initiating treatment with methotrexate with corticosteroids over corticosteroids alone and azathioprine or mycophenolate in combination with corticosteroids ○ Severe disease: ▪ Conditional recommendation of initiating treatment with rituximab over cyclophosphamide ▪ Either IV pulse corticosteroids or oral high-dose corticosteroids may be prescribed as part of initial therapy • Maintenance:

	○ Recommend treatment with methotrexate or azathioprine for maintenance of remission ○ Patients with severe disease that entered remission on cyclophosphamide or rituximab, rituximab is conditionally recommended over treatment with methotrexate or azathioprine for maintenance of remission ○ Patients with severe disease that entered remission on cyclophosphamide or rituximab, methotrexate or azathioprine are conditionally recommended over treatment with mycophenolate or leflunomide for maintenance of remission Treatment resistance in GPA is defined as the presence of active disease affecting that is organ or light threatening despite optimal initial immunosuppressive therapy with glucocorticoids plus either cyclophosphamide or rituximab for an adequate period of time (usually 6 months or 3 months in a patient who is dialysis dependent). Treatment resistant disease is diagnosed if either progressive kidney decline plus persistent active urine sediment that is judged to be due to active vasculitis or a kidney biopsy shows active glomerulonephritis is present, or persistence or new appearance of extrarenal manifestations of active vasculitis are present.(28) The first step for management of treatment resistant GPA is to ensure that the clinical abnormalities are not due to drug toxicity, nonadherence, an inadequate regimen, progression of chronic inactive disease, infection, and/or pathogenic processes other than ongoing inflammation. Treatment strategy is dependent on initial induction therapy, whether cyclophosphamide or rituximab was used, then the other agent is tried for treatment resistant GPA. If both agents have been tried and failed after at least three to six months of therapy, or there are contraindications to cyclophosphamide and rituximab, then mycophenolate mofetil is the next recommended option.(28) The ACR guidelines recommend the following treatment options for patients with relapsed disease or refractory disease:(28) • Relapsed: ○ Patients not on rituximab for maintenance therapy, conditional recommendation to initiate rituximab over cyclophosphamide for re-induction therapy ○ Patients currently treated with rituximab for maintenance therapy, conditionally recommend switching to cyclophosphamide over receiving additional rituximab for re-induction therapy • Refractory disease: ○ Patients with severe disease that is refractory to cyclophosphamide or rituximab, conditional recommendation to switch to the other agent over combining the two therapies ○ Patients with refractory to induction therapy, conditional recommendation to add IVIG to current therapy The role of anti-TNF therapy has unproven efficacy for GPA and should only be attempted in patients that are resistant to cyclophosphamide, rituximab, and mycophenolate mofetil. Infliximab was studied in an open label study with 16 patients with acute ANCA-associated vasculitis at first presentation or relapse and in 16 patients with persistent disease despite multiple immunosuppressive regiments. Serious infections and deaths were reported despite remission achieved in 14 patients of each group.(26)
NON-ONCOLOGY-Pemphigus vulgaris	Pemphigus encompasses a spectrum of rare mucocutaneous bullous diseases that are autoimmune in origin. Due to the rarity of these diseases, it can take patients months before being diagnosed with pemphigus, during which time many are treated for other blistering diseases. Even once the diagnosis is made, treatment regimens can vary greatly as there is no defined standard of care due to the paucity of large-scale clinical trials evaluating their efficacy.(14)

	The objectives of therapeutic management of PV are to promote healing of blisters and erosions, improve functional status, prevent/strictly limit development of new blisters and erosions, improve quality of life, and to limit common side-effects usually associated with long-term immunosuppressive or corticosteroid treatment.(14) First-line treatment of PV includes corticosteroids, rituximab, azathioprine, mycophenolate mofetil, and cyclophosphamide. Although systemic glucocorticoid therapy is effective, the high doses and long treatment periods that are needed to maintain the clinical response may lead to serious or life-threatening side effects. A nonsteroidal systemic immunomodulatory medication is often used as an adjunct to systemic glucocorticoid therapy. Rituximab has shown superior efficacy and safety compared to standard dose systemic corticosteroids initially with slow tapering of the corticosteroids (see efficacy section).(14)
NON-ONCOLOGY-Efficacy	Rituximab is a monoclonal antibody directed against CD20 antigen. It binds to the antigen CD20 on pre-B and mature B lymphocytes. B cells are thought to play a role in the pathogenesis of rheumatoid arthritis (RA). The B cells may act at several sites in the autoimmune/inflammatory process including production of rheumatoid factor (RF), T-cell activation, and proliferation of cytokine production.(1)
NON-ONCOLOGY-Efficacy: Rheumatoid Arthritis	Efficacy of rituximab for initial and re-treatment in patients with moderate to severe active RA who had a previous inadequate response to at least one anti-tumor necrosis factor (TNF) biologic was evaluated in two randomized, double-blind, placebo-controlled trials. The trials enrolled subjects who were 18 years of age or older with a diagnosis of active RA. Efficacy endpoints were similar between the trials. Both trials evaluated the proportion of patients with an ACR 20, 50, and 70 responses at week 24 with the second trial also evaluating the re-treatment course at Week 48. A higher proportion of patients achieved an ACR 20 response through Week 24 with a similar pattern shown for ACR 50 and 70.(1)
NON-ONCOLOGY-Efficacy: Granulomatosis with Polyangiitis (GPA) (Wegner's Granulomatosis) and Microscopic Polyangiitis (MPA)	197 patients with active, severe GPA and MPA were treated in a randomized, double-blind, active controlled multicenter non-inferiority study, conducted in two phases- a 6-month remission induction phase and a 12-month remission maintenance phase. Patients were diagnosed using the Chapel Hill Consensus conference criteria. In the remission induction phase, 99 patients received Rituxan 375 mg/m^2 once weekly for 4 weeks and 98 patients received oral cyclophosphamide 2 mg/kg daily for 3 to 6 months. Once remission was achieved or at the end of the 6-month remission induction period, patients in the cyclophosphamide arm received azathioprine to maintain remission. The patients in the Rituxan arm did not receive additional therapy to maintain remission. The main outcome measure for both GPA and MPA patients was achievement of complete remission at 6 months defined as a Birmingham Vasculitis Activity Score for Granulomatosis with Polyangiitis score of 0 and the patients were off glucocorticoid therapy. The pre-specified non-inferiority margin was a treatment difference of 20%. The study demonstrated non-inferiority of Rituxan to cyclophosphamide for complete remission at 6 months with a 64% complete remission in the Rituxan arm compared to 53% complete remission in the cyclophosphamide arm.(1)
NON-ONCOLOGY-Efficacy: Pemphigus vulgaris (PV)	Non-U.S.-licensed rituximab in combination with short-term prednisone was compared to prednisone monotherapy as first-line treatment in 90 newly diagnosed adult patients with moderate to severe pemphigus in a randomized, open-label, controlled, multicenter study. The primary endpoint for the study was complete remission (complete epithelialization and absence of new and/or established lesions at Month 24 without the use of prednisone therapy for 2 months or more. 89% of patients in the non-U.S. licensed rituximab + short term prednisone group had a complete response and 34% of the prednisone only group had a complete response.(1)
NON-ONCOLOGY-Safety	Riabni (rituximab-arrx), Rituxan (rituximab), Ruxience (rituximab-pvvr), and Truxima (rituximab-abbs) contain boxed warnings for serious, sometimes fatal infusion reactions. Approximately 80% of fatalities due to these infusion reactions are associated with the first infusion. Additional boxed warnings include hepatitis B virus (HBV) reactivation (some cases resulting in fulminant hepatitis, hepatic failure, and death), severe (including fatal) mucocutaneous reactions, and progressive multifocal leukoencephalopathy (PML) resulting in death.(1,6,7,25)

	Rituxan Hycela (rituximab and hyaluronidase human) contains a boxed warning for severe mucocutaneous reactions (some with fatal outcomes), hepatitis B virus reactivation (in some cases resulting in fulminant hepatitis, hepatic failure, and death), and progressive multifocal leukoencephalopathy resulting in death.(2) Riabni (rituximab-arrx), Rituxan (rituximab), Rituxan Hycela (rituximab and hyaluronidase human), Ruxience (rituximab-pvvr), and Truxima (rituximab-abbs) have no FDA labeled contraindications for use.(1,2,6,7,25)
NON-ONCOLOGY-Compendia Supported Indications	For the purposes of the non-oncology criteria, indications deemed appropriate are those that are supported by AHFS, DrugDex level of evidence 1 or 2a. In addition, this criteria will allow for use for use in post-transplant lymphoproliferative disorder, both relapsing and primary progressive forms of multiple sclerosis, and neuromyelitis optica spectrum disorder based on relevant clinical studies.
NON-ONCOLOGY-Compendia Supported Indications: Multiple Sclerosis	Multiple sclerosis (MS) is a disorder of the central nervous system (CNS) characterized by demyelization, inflammation, and degenerative changes. Most people with MS experience relapses and remissions of neurological symptoms, particularly early in the disease, and clinical events are usually associated with areas of CNS inflammation. Gradual worsening or progression, with or without subsequent acute attacks of inflammation or radiological activity, may take place early, but usually becomes more prominent over time. While traditionally viewed as a disease solely of CNS white matter, more advanced imaging techniques have demonstrated significant early and ongoing CNS gray matter damage as well.(10) Those diagnosed with MS may have many fluctuating and disabling symptoms (including, but not limited to, fatigue, impaired mobility, mood and cognitive changes, pain and other sensory problems, visual disturbances, and elimination dysfunction), resulting in a significant impact on quality of life for patients and their families. Diagnosis of MS is primarily based on clinical presentation. The core requirement for the diagnosis is demonstration of CNS lesion dissemination and presence of symptoms such as visual loss, motor function loss, difficulty with balancing, and vertigo. There are currently four major types of MS: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS).(10) Both the Multiple Sclerosis Coalition and the American Academy of Neurology recommend initiating treatment with a DMA FDA approved for the patient's phenotype as soon as possible following the diagnosis of multiple sclerosis. There are several DMAs with at least 10 mechanisms of action available to people with MS. The factors affecting choice of therapy at any point in the disease course are complex and must be appropriately analyzed and addressed through a shared decision-making process between the individual and the treating clinician.(10,11) There is a subgroup of RRMS patients who have a more aggressive disease course marked by a rapid accumulation of physical and cognitive deficit, despite treatment with 1 or more DMTs. In the past, this disease phenotype was called aggressive MS; it is now called highly active MS. It is generally agreed that the severe nature of this phenotype requires different treatment decisions. There is no consensus on the definition of highly active MS or the treatment algorithm.(24) The National Institute for Health and Care Excellence (NICE) defines rapidly evolving severe RRMS as two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI.(12) The Multiple Sclerosis Coalition recommends that clinicians should consider prescribing a high efficacy medication such as alemtuzumab, cladribine, fingolimod, natalizumab or ocrelizumab for newly diagnosed individuals with highly active MS. Clinicians should also consider prescribing a high efficacy medication for individuals who have breakthrough activity on another DMA regardless of the number of previously used agents.(10) The American Academy of Neurology has recommended alemtuzumab, fingolimod, and natalizumab as options for patients with MS with highly active MS.(11)

	Lack of response to DMAs is hard to define, as most patients with MS are not free of all disease activity. Relapses or new MRI detected lesions may develop after initiation of a DMA and before the treatment becomes effective for patients. When determining efficacy, sufficient time for the DMA therapy to take full effect and patient adherence are important considerations. Evidence of one or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination while being treated with a DMA for a 1 year period suggests a sub-optimal response, an alternative regimen (e.g., different mechanism of action) should be considered to optimize therapeutic benefit.(29) A National MS Society consensus statement recommends changing from one disease modifying therapy to another only for medically appropriate reasons (e.g. lack of efficacy, adverse effects, or if better treatments options become available).(10) A 2016 Institute for Clinical and Economic Review (ICER) report included rituximab as treatment for both relapsing forms and progressive forms of MS based on feedback from practicing clinicians, specialty societies, manufacturers, and payors. The results of the ICER evaluation on the use of rituximab for MS showed that the evidence is promising and recommend rituximab as an option for treating MS.(13)
NON-ONCOLOGY-Compendia Supported Indications: Neuromyelitis Optica Spectrum Disorder	Neuromyelitis optica spectrum disorder (NMOSD), also known as Devic disease, is a chronic disorder of the brain and spinal cord dominated by inflammation of the optic nerve (optic neuritis) and inflammation of the spinal cord (myelitis). Classically, it was felt to be a monophasic illness, consisting of episodes of inflammation of one or both optic nerves and the spinal cord over a short period of time (days or weeks) but, after the initial episode, no recurrence. It is now recognized that most patients satisfying current criteria for NMOSD experience repeated attacks separated by periods of remission. The interval between attacks may be weeks, months or years.(19) Early in the course of the disease, it may be difficult to distinguish between NMOSD and multiple sclerosis because both may cause optic neuritis and myelitis as symptoms. However, the optic neuritis and myelitis tend to be more severe in NMOSD; the brain MRI is more commonly normal, and the spinal fluid analysis does not usually show oligoclonal bands in NMOSD, which are features that help distinguish it from MS.(19) NMOSD can be AQP4 antibody positive or negative. The diagnostic criteria for NMOSD with AQP4 positive diagnosis are as follows: at least 1 core clinical characteristic, a positive test for AQP4-IgG, and exclusion of alternative diagnoses. The core clinical characteristics are as follows:(21) • Optic neuritis • Acute myelitis • Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting • Acute brainstem syndrome • Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions • Symptomatic cerebral syndrome with NMOSD-typical brain lesions An international consensus panel reached several conclusions in addition to the above criteria to establish a NMOSD diagnosis. First, at least 1 discrete clinical attack of CNS symptoms must occur to establish NMOSD diagnosis. Although asymptomatic AQP4-IgG seropositive status may exist for years before clinical NMOSD presentation, the natural history of asymptomatic seropositivity is poorly understood. Second, NMOSD diagnosis is not warranted in asymptomatic patients with NMOSD-compatible MRI lesions because the expected clinical course in such individuals is unknown. Third, no clinical characteristic is pathognomonic of NMOSD. Accordingly, a single clinical manifestation is not diagnostic when AQP4-IgG is not detected. Finally, no single characteristic is exclusionary, but some are considered red flags that signal the possibility of alternative diagnoses. The main clinical red flags concern the temporal course of the syndrome rather than the actual manifestations. Most notably, a gradually progressive course of neurologic worsening over months to years is very

	uncommon (1%–2%) in NMOSD. However, after thorough investigation for potential competing disorders, the weight of evidence may justify NMOSD diagnosis despite presence of 1 or more red flags.(21) Treatment strategies for attack prevention in NMOSD and MS differ. Some MS immunotherapies appear to aggravate NMOSD, indicating an imperative for early, accurate diagnosis. Patients with NMOSD who are AQP4-IgG seropositive should be assumed to be at risk for relapse indefinitely and preventive treatment should be considered.(8) Azathioprine and mycophenolate mofetil have been used off label to prevent NMOSD attacks for decades. Their efficacy in NMOSD has been demonstrated in several retrospective studies and case series. In recent years, their use in NMOSD has declined in favor of rituximab owing to their comparative lower efficacy as demonstrated in multiple retrospective studies.(30) Rituximab is one of the most commonly used off-label preventative therapies in NMOSD. Rituximab is a monoclonal antibody (MAB) against CD20-positive B-Cells with include pre B-cell, immature B-cell, and memory B-cell lineage but not plasmablasts or plasma cells. Its exact mechanism of action in NMOSD is unknown but is hypothesized to involve reduction of pathogenic antibody production, dampening of pro-inflammatory cytokines, and decreasing B-cell dependent antigen presentation to T-cells.(30) Eculizumab, ineblizumab, satralizumab, and ravulizumab are FDA labeled therapies that can be used as monotherapy for NMOSD.(30) Disability in NMO is a direct consequence of the relapse. Spontaneous gradual progression of disability like in MS is very rare in NMO. Thus, NMO relapses are a clinically relevant measure. Amongst secondary end points, disability is very important. The main categories are spinal cord/ brainstem related, motor (weakness, spasticity), sensory (numbness and pain), bladder, bowel, sexual function, and vision. EDSS is suitable and well validated in MS research, but cerebellar and cerebral functional scales are not really applicable in NMO, as cognitive and cerebellar dysfunction is limited in NMO. The Optic Spinal Impairment Scale is derived and modified from EDSS. There are no formal psychometrics supporting the scale and it is not widely used. There are numerous vision specific scales, but none are specific for optic neuritis.(22)
NON-ONCOLOGY-Compendia Supported Indications: Cold Agglutinin Disease	Autoimmune hemolytic anemias (AIHAs) are relatively uncommon clinicopathological entities characterized by the production of autoantibodies directed against surface antigens on red blood cells (RBCs). AIHAs are generally classified as warm, cold, or mixed type, depending on the optimum temperature at which the autoantibodies bind surface antigens. Warm and cold autoantibodies can be either idiopathic (primary) or due to an underlying condition (secondary). Cold AIHAs can be further characterized as follows:(31) • Primary chronic cold agglutinin disease (CAD) • Paroxysmal cold hemoglobinuria • Secondary cold AIHAs associated with an underlying condition, e.g., cold AIHAs associated with an underlying condition, such as infection or malignancy. In general, cold agglutinins react at temperatures well below physiologic temperature, usually 0-4 degrees Celsius, which may cause agglutination in the nose, ears, or fingers of patients, leading to painful cold induced symptoms. Approximately 90% of CAD patients have immunoglobulin M (IgM) – mediated disease, while IgG and IgA – mediated cases are rarely reported.(31) The hemolysis in CAD is complement-mediated and can be intravascular or extravascular. Complement activation has been shown to occur in two steps, one of which is temperature dependent. As blood circulates through the extremities and cooler skin, which can be as cool as 28-30 degrees Celsius, cold agglutinins transiently bind the erythrocyte surface. As the erythrocytes with the bound Ig-C1 complex

	circulate back to warmer areas of the body, C1q esterase activates C4 and C2, which generates the C3 convertase. This step is temperature-dependent, as C4 requires higher temperatures to be enzymatically active. C3 convertase cleaves C3 into C3a and C3b. Erythrocytes coated with C3b are sequestered by macrophages in the reticuloendothelial system, particularly Kupffer's cells in the liver. Sequestration ultimately leads to destruction of these cells and extravascular hemolysis. However, C3b can be further cleaved into C3c and C3d. C3d is found in large quantities on the surface of erythrocytes in patients with CAD, occupying potential binding sites for C4 and C3, preventing hemolysis of the patient's own cells. Transfused cells, however, are not coated by C3d and are susceptible to complement activation and hemolysis. If complement activation goes past the C3 step, the membrane attack complex with C5b-C9 may form, leading to intravascular hemolysis.(31)
	
	Primary CAD should be considered in elderly patients with unexplained chronic anemia with or without associated cold-induced symptoms. The most common presenting symptom is acrocyanosis, which is a dark purple to gray discoloration of the skin when exposed to the cold in the acral areas, such as the fingertips, toes, nose, and ears and is found in 44% of patients. Other cold-induced symptoms, such as Raynaud phenomenon, were reported in another 39% of patients. These symptoms may wax and wane throughout a patient's course of disease. However, in rare cases, progression of acrocyanosis to skin necrosis has been reported.(31)
	
	There are multiple definitions in the literature as to what is required to make the diagnosis of CAD including:(31)
	
	• Hemolysis labs
	  ○ Decreased hemoglobin
	  ○ Increased bilirubin
	  ○ Increased LDH
	  ○ Decreased haptoglobin
	
	• Cold-agglutinin specific labs (in sequential order)
	  ○ Polyspecific DAT positive
	  ○ C3d DAT positive
	  ○ Cold agglutinin titer greater than or equal to 1:64 at 4 degrees Celsius
	
	Since cold agglutinins bind in colder temperatures, patients are generally counseled to keep warm, particularly their head, face, and extremities. This has been shown to alleviate symptoms and may prevent severe exacerbations of hemolytic anemia. These findings are, however, of low-quality evidence. Practically, it is unreasonable to expect a patient to constantly remain warm, and especially in winter months.(31)
	
	Symptomatic anemia can be treated with RBC transfusion. Blood bank testing for underlying alloantibodies and crossmatch testing should be performed at 37 degrees Celsius. It is important to note, though, that cold agglutinins can cause interference with laboratory testing, such as ABO blood typing results and hematocrit levels in a CBC.(31)
	
	Despite the importance of cold avoidance, approximately 70% of patients require pharmacological treatment. The most common reason for treatment is chronic anemia. Patients are generally started on corticosteroids, though the benefit of this practice has not been supported in the literature. Although corticosteroids are a rapid and effective treatment for warm AIHAs, they have not been shown to be as effective in CAD. Retrospective studies have found that less than 15% of patients respond to corticosteroids, and they require higher doses to maintain remission.(31)

	Rituximab has been used to treat CAD since the late 1990s. Studies have shown that 45-60% of patients completely respond or partially respond to monotherapy with rituximab, with a median time to response of 3 months. Although monotherapy with rituximab has been relatively successful, some studies have examined the effectiveness of combining a second drug, such as fludarabine, to increase the efficacy of treatment. A prospective, uncontrolled study showed a 76% response rate to the combination therapy.(31)
NON-ONCOLOGY-Compendia Supported Indications: Generalized Myasthenia Gravis	Myasthenia gravis (MG) is a neuromuscular disorder primarily characterized by muscle weakness and muscle fatigue. Although the disorder usually becomes apparent during adulthood, symptom onset may occur at any age. The condition may be restricted to certain muscle groups, particularly those of the eyes (ocular myasthenia), or may become more generalized (generalized myasthenia gravis [gMG]), involving multiple muscle groups. Most individuals with MG develop weakness and drooping of the eyelids (ptosis); weakness of eye muscles, resulting in double vision (diplopia); and excessive muscle fatigue following activity. Additional features commonly include weakness of facial muscles; impaired speech (dysarthria); difficulties chewing and swallowing (dysphagia); and weakness of the upper arms and legs (proximal limb weakness). In addition, in about 10% of patients, affected individuals may develop potentially life-threatening complications due to severe involvement of muscles used during breathing (myasthenic crisis). MG results from an abnormal immune reaction in which antibodies inappropriately attack and gradually injure certain receptors in muscles that receive nerve impulses (antibody-mediated autoimmune response).(33) The course of MG is highly variable. For example, the degree of muscle weakness may vary over hours, from day to day, or over weeks and months, tending to increase with repeated muscle use and to improve with rest. In addition, particularly during the first years after disease onset, some affected individuals may experience alternating periods in which symptoms temporarily subside or worsen. A short-term aggravation of symptoms may be triggered by a variety of factors, including infection, excessive physical activity, menstruation, and after delivery of a child.(33) Corticosteroids are a standard treatment for MG but may cause transient worsening within the first 2 weeks and patients should be monitored closely for this possibility. Because of this a MG consensus panel lists corticosteroids as one of many agents to avoid or use with caution in MG. A nonsteroidal immunosuppressive agent should be used initially in treating MG. Nonsteroidal immunosuppressive agents that can be used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. For nonsteroidal immunosuppressive agents, once treatment goals have been achieved and maintained for 6 months to 2 years, the immunosuppressive dose should be tapered slowly to the minimal effective amount. Patients must be monitored for potential adverse effects and complications from immunosuppressive drugs. Changing to an alternative immunosuppressive agent should be considered if adverse effects and complications are medically significant or create undue hardship for the patient.(34) Plasma exchange and IVIg are appropriately used as short-term treatments in patients with MG with life-threatening signs such as respiratory insufficiency or dysphagia; in preparation for surgery in patients with significant bulbar dysfunction; when a rapid response to treatment is needed; when other treatments are insufficiently effective; and prior to beginning corticosteroids if deemed necessary to prevent or minimize exacerbations. The use of IVIg as maintenance therapy can be considered for patients with refractory MG or for those in whom immunosuppressive agents are contraindicated. Refractory MG is defined as post-intervention status is unchanged or worse after corticosteroids and at least 2 other immunosuppressive agents, used in adequate doses for an adequate duration, with persistent symptoms or side effects that limit functioning, as defined by the patient and physician.(34) Certain medications have established pharmacologic adverse effects on neuromuscular transmission. Use of these medications in a patient with MG can further reduce the effectiveness of neuromuscular transmission and cause increased clinical weakness. However, reported associations do not necessarily mean these medications should never be prescribed in MG. Clinical judgment and the risk-to-benefit ratio of the drug

	should be considered when it is deemed important for a patient's treatment. Medications that can cause a significant increase in weakness in patients with MG include fluoroquinolones, botulinum toxin, ketolides (particularly telithromycin) and aminoglycoside antibiotics, beta blockers, macrolide antibiotics, procainamide, quinidine, quinine, and magnesium. A number of other medications may unmask or exacerbate MG, particularly the neuromuscular blocking agents used during anesthesia, which can lead to prolonged postoperative weakness and ventilator dependence.(34)

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POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Q5123	Riabni	rituximab-arrx iv soln	100 MG/10ML ; 500 MG/50ML	M ; N ; O ; Y	N		
J9312	Rituxan	rituximab iv soln	100 MG/10ML ; 500 MG/50ML	M ; N ; O ; Y	N		
J9311	Rituxan hycela	rituximab-hyaluronidase human inj	1400-23400 MG -UT/11.7ML ; 1600-26800 MG -UT/13.4ML	M ; N ; O ; Y	N		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Riabni	rituximab-arrx iv soln	100 MG/10ML ; 500 MG/50ML	Commercial ; HIM ; ResultsRx
Rituxan	rituximab iv soln	100 MG/10ML ; 500 MG/50ML	Commercial ; HIM ; ResultsRx
Rituxan hycela	rituximab-hyaluronidase human inj	1400-23400 MG -UT/11.7ML ; 1600-26800 MG -UT/13.4ML	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Non-Oncology	**Non-Oncology Initial Evaluation** **Preferred Agent(s)** **Ruxience** (rituximab-pvvr) **Truxima** (rituximab-abbs) **Non-Preferred Agent(s)** **Riabni** (rituximab-arrx) **Rituxan** (rituximab) **Rituxan Hycela** (rituximab and hyaluronidase human) **Target Agent(s)** will be approved when ALL of the following are met: 1. The requested agent is being used for a non-oncology indication (refer to the Rituximab Oncology policy for oncology indications. Note: Rituxan Hycela is not indicated for non-oncologic diagnoses) **AND** 2. ONE of the following: A. The patient has a diagnosis of moderate to severely active rheumatoid arthritis (RA) AND ALL of the following: 1. ONE of the following: A. The patient has tried and had an inadequate response to maximally tolerated methotrexate (e.g., titrated to 25 mg weekly) after at least a 3-month duration of therapy **OR** B. The patient has tried and had an inadequate response to another conventional agent (i.e., hydroxychloroquine, leflunomide, or sulfasalazine) used in the treatment of RA after at least a 3-month duration of therapy **OR** C. The patient has an intolerance or hypersensitivity to ONE of the following conventional agents (i.e., maximally tolerated methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR** D. The patient has an FDA labeled contraindication to ALL conventional agents (i.e., methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR** E. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of RA **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to at least one biologic immunomodulator FDA labeled or supported in compendia for the treatment of RA after at least a 3-month duration of therapy **OR** B. The patient has an intolerance or hypersensitivity to ONE biologic immunomodulator FDA labeled for the treatment of RA **OR** C. The patient has an FDA labeled contraindication to ALL biologic immunomodulators FDA labeled for the treatment of RA **AND** 3. ONE of the following (please refer to "Immunomodulatory Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitor, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following:

Module	Clinical Criteria for Approval
	1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for the use of combination therapy (copy of support required, i.e., clinical trials, phase III studies, guidelines) **OR** B. The patient has a diagnosis of granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) OR Microscopic polyangiitis (MPA) AND BOTH of the following: 1. ONE of the following: A. The patient will be using a corticosteroid in combination with the requested agent **OR** B. The patient has an intolerance or hypersensitivity to at least ONE corticosteroid used for the treatment of GPA or MPA **OR** C. The patient has an FDA labeled contraindication to at least ONE corticosteroid used for the treatment of GPA or MPA **AND** 2. ONE of the following (please refer to "Immunomodulatory Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitor, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for the use of combination therapy (copy of support required, i.e., clinical trials, phase III studies, guidelines) **OR** C. The patient has a diagnosis of myasthenia gravis AND ONE of the following: 1. The patient has tried and had an inadequate response to previous treatment (e.g., corticosteroids, immunosuppressants [e.g., azathioprine], plasma exchange, IV immunoglobulin, thymectomy) **OR** 2. The patient has an intolerance or hypersensitivity to corticosteroids or immunosuppressants (e.g., azathioprine) **OR** 3. The patient has an FDA labeled contraindication to BOTH a corticosteroid AND an immunosuppressant (e.g., azathioprine) **OR** D. The patient has a diagnosis of post-transplant lymphoproliferative disorder **OR** E. The patient has a diagnosis of moderate to severe pemphigus vulgaris (PV) **OR** F. The patient has a diagnosis of a relapsing form of multiple sclerosis (MS) AND the patient will NOT be using the requested agent in combination with an additional disease modifying agent (DMA) for the requested indication **OR** G. The patient has a diagnosis of primary progressive form of multiple sclerosis AND the patient will NOT be using the requested agent in combination with an additional disease modifying agent (DMA) for the requested indication **OR** H. The patient has a diagnosis of neuromyelitis optica spectrum disorder (NMOSD) AND ALL of the following: 1. The diagnosis was confirmed by at least ONE of the following: A. Optic neuritis **OR** B. Acute myelitis **OR** C. Area postrema syndrome (episode of otherwise unexplained hiccups or nausea and vomiting) **OR** D. Acute brainstem syndrome **OR** E. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions **OR** F. Symptomatic cerebral syndrome with NMOSD-typical brain lesions **AND**

Module	Clinical Criteria for Approval
	2. The patient has had at least 1 discrete clinical attack of CNS symptoms **AND** 3. Alternative diagnoses (e.g., multiple sclerosis, ischemic optic neuropathy) have been ruled out **AND** 4. The patient will NOT be using the requested agent in combination with Enspryng, Soliris, Ultomiris, or Uplizna for the requested indication **OR** I. The patient has a diagnosis of cold agglutinin disease (CAD) AND ALL of the following: 1. The diagnosis was confirmed by ALL of the following: A. Chronic hemolysis **AND** B. Positive polyspecific direct antiglobulin test (DAT) **AND** C. Positive monospecific DAT specific for C3d **AND** D. Cold agglutinin titer greater than or equal to 64 at 4 degrees Celsius **AND** E. IgG DAT less than or equal to 1+ **AND** 2. The patient has had at least one red blood cell transfusion in the last 6 months **AND** 3. The patient has a baseline hemoglobin (before treatment for the diagnosis) of less than 10 g/dL **OR** J. The patient has another FDA labeled indication for the requested agent **OR** K. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 3. If the client has preferred agents, then ONE of the following: A. The requested agent is a preferred agent **OR** B. The patient has tried and had an inadequate response to TWO preferred agents that is NOT expected to occur with the requested agent (medical records required) **OR** C. The patient has an intolerance or hypersensitivity to TWO preferred agents that is NOT expected to occur with the requested agent (medical records required) **OR** D. The patient has an FDA labeled contraindication to ALL preferred agents that is NOT expected to occur with the requested agent (medical records required) **AND** 4. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested agent for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 7. The patient has been screened for hepatitis B infection measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) **AND** 8. If the patient is positive for hepatitis B, then the patient has begun hepatitis B therapy **AND** 9. ONE of the following: A. The requested quantity (dose) is within the FDA labeled dosing or compendia supported dosing for the requested indication **OR** B. There is support for therapy with a higher dose for the requested indication **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** • 1 month for refractory myasthenia gravis • 12 months for all other diagnoses

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	Non-Oncology Renewal Evaluation: **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Medical Drug Review process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. ONE of the following: A. The patient has a diagnosis of moderate to severely active rheumatoid arthritis (RA) AND ONE of the following (please refer to "Immunomodulatory Agents NOT to be used Concomitantly" table): 1. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitor, JAK inhibitors, IL-4 inhibitors) **OR** 2. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: A. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** B. There is support for combination therapy (copy of support required, i.e., clinical trials, phase III studies, guidelines) **OR** B. The patient has a diagnosis of granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) OR Microscopic polyangiitis (MPA) AND ONE of the following (please refer to "Immunomodulatory Agents NOT to be used Concomitantly" table): 1. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitor, JAK inhibitors, IL-4 inhibitors) **OR** 2. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: A. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** B. There is support for combination therapy (copy of support required, i.e., clinical trials, phase III studies, guidelines) **OR** C. The patient has a diagnosis of a relapsing form of multiple sclerosis (MS) AND the patient will NOT be using the requested agent in combination with an additional disease modifying agent (DMA) for the requested indication (please refer to "MS DMA Agents Contraindicated" table) **OR** D. The patient has a diagnosis of primary progressive form of multiple sclerosis AND the patient will NOT be using the requested agent in combination with an additional disease modifying agent (DMA) for the requested indication (please refer to "MS DMA Contraindicated" table **OR** E. The patient has a diagnosis of neuromyelitis optica spectrum disorder (NMOSD), AND the patient will NOT be using the requested agent in combination with Enspryng, Soliris, Ultomiris or Uplizna **OR** F. The patient has another diagnosis **AND** 3. The patient has shown clinical benefit (i.e., slowing of disease progression or decrease in symptom severity and/or frequency) with the requested agent **AND** 4. If the client has preferred agents, then ONE of the following: A. The requested agent is a preferred agent **OR** B. The patient has tried and had an inadequate response to TWO preferred agents that is NOT expected to occur with the requested agent (medical records required) **OR** C. The patient has an intolerance or hypersensitivity to TWO preferred agents that is NOT expected to occur with the requested agent (medical records required) **OR** D. The patient has an FDA labeled contraindication to ALL preferred agents that is not expected to occur with the requested agent (medical records required) **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 7. ONE of the following:

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	A. The requested quantity (dose) is within the FDA labeled dosing or compendia supported dosing for the requested indication **OR** B. There is support for therapy with a higher dose for the requested indication **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** Up to 12 months
Oncology	**Preferred Agent(s)** **Ruxience** (rituximab-pvvr) **Truxima** (rituximab-abbs) **Non-Preferred Agent(s)** **Riabni** (rituximab-arrx) **Rituxan** (rituximab) **Rituxan Hycela** (rituximab and hyaluronidase human) **Target Agent(s)** will be approved for oncologic uses when ALL following are met: 1. The requested agent is being used for an oncology indication (see the Rituximab Non-Oncology module for non-oncology indications. Note: Rituxan Hycela is not indicated for non-oncologic diagnoses) **AND** 2. ONE of the following: A. The patient has a diagnosis of relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma (NHL) AND ONE of the following: 1. The requested agent will be used as a single agent **OR** 2. The requested indication is supported by ALL requirements in either FDA labeling or compendia support for the requested agent (i.e., this indication must be supported by ALL requirements in the FDA label or compendia support [e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy, etc.]) **OR** B. The patient has a diagnosis of previously untreated follicular, CD20-positive, B-cell non-Hodgkin's lymphoma (NHL) AND ONE of the following: 1. The requested agent will be used for initial therapy AND the requested agent will be used in combination with first line chemotherapy **OR** 2. The requested agent will be used for maintenance therapy AND BOTH of the following: A. The patient achieved complete or partial response to rituximab in combination with chemotherapy **AND** B. The requested agent will be used as a single-agent **OR** 3. The requested indication is supported by ALL requirements in either FDA labeling or compendia support for the requested agent (i.e., this indication must be supported by ALL requirements in the FDA label or compendia support [e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy, etc.]) **OR** C. The patient has a diagnosis of non-progressing (including stable disease), low-grade CD20-positive, B-cell non-Hodgkin's lymphoma (NHL) AND ONE of the following: 1. BOTH of the following: A. The requested agent will be used after first-line CVP (cyclophosphamide, vincristine, prednisone) chemotherapy **AND** B. The requested agent will be used as a single agent **OR** 2. The requested indication is supported by ALL requirements in either FDA labeling or compendia support for the requested agent (i.e., this indication must be supported by ALL requirements in the FDA label or NCCN compendia support [e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy, etc.]) **OR** D. The patient has a diagnosis of previously untreated diffuse large B-cell, CD20-positive non-Hodgkin's lymphoma (NHL) AND ONE of the following:

Module	Clinical Criteria for Approval
	1. The requested agent will be used in combination with CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone] regimen **OR** 2. The requested agent will be used in another anthracycline-based chemotherapy regimen **OR** 3. The requested indication is supported by ALL requirements in either FDA labeling or compendia support for the requested agent (i.e., this indication must be supported by ALL requirements in the FDA label or compendia support [e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy, etc.]) **OR** E. The patient has a diagnosis of previously untreated, advanced stage, CD20-positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), Burkitt-like lymphoma (BLL), or mature B-cell acute leukemia (B-AL) AND ONE of the following: 1. The patient will use in combination with chemotherapy **OR** 2. The requested indication is supported by ALL requirements in either FDA labeling or compendia support for the requested agent (i.e., this indication must be supported by ALL requirements in the FDA label or compendia support [e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy, etc.]) **OR** F. The patient has a diagnosis of CD20-positive Chronic lymphocytic leukemia (CLL) AND ONE of the following: 1. The requested agent will be used in combination with fludarabine and cyclophosphamide (FC) **OR** 2. The requested indication is supported by ALL requirements in either FDA labeling or compendia support for the requested agent (i.e., this indication must be supported by ALL requirements in the FDA label or compendia support [e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy, etc.]) **OR** G. The patient has a diagnosis of another FDA labeled indication for the requested agent (i.e., this indication must be supported by ALL requirements in the FDA label [e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy]) **OR** H. The patient has a compendia supported indication for the requested agent (i.e., this indication must be supported by ALL requirements in the compendia support [e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy, etc.]) **AND** 3. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within the FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 4. If the client has preferred agents, then ONE of the following: A. The requested agent is a preferred agent **OR** B. The patient has tried and had an inadequate response to TWO preferred agents (medical records required) **OR** C. The patient has an intolerance or hypersensitivity to TWO preferred agents that is NOT expected to occur with the requested agent (medical records required) **OR** D. The patient has an FDA labeled contraindication to ALL preferred agents that is NOT expected to occur with the requested agent (medical records required) **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 6. The patient has been screened for hepatitis B infection measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) **AND** 7. If the patient is positive for hepatitis B, then the patient has begun hepatitis B therapy **AND** 8. ONE of the following: A. The requested quantity (dose) is within FDA labeled dosing or compendia supported dosing for the requested indication **OR**

Module	Clinical Criteria for Approval
	B. There is support for therapy with a higher dose for the requested indication **Compendia Allowed:** NCCN 1 or 2a recommended use **Length of Approval:** 12 months or for duration of treatment as supported in FDA labeling or compendia, whichever is shorter.

CONTRAINDICATION AGENTS

Contraindicated as Concomitant Therapy
MS Disease Modifying Agents Aubagio (teriflunomide) Avonex (interferon b-1a) Bafiertam (monomethyl fumarate) Betaseron (interferon b-1b) Briumvi (ublituximab-xiiy) Copaxone (glatiramer) dimethyl fumarate Extavia (interferon b-1b) fingolimod Gilenya (fingolimod) glatiramer Glatopa (glatiramer) Kesimpta (ofatumumab) Lemtrada (alemtuzumab) Mavenclad (cladribine) Mayzent (siponimod) Ocrevus (ocrelizumab) Ocrevus Zunovo (ocrelizumab-hyaluronidase) Plegridy (peginterferon b-1a) Ponvory (ponesimod) Rebif (interferon b-1a) Tascenso ODT (fingolimod) Tecfidera (dimethyl fumarate) teriflunomide Tysabri (natalizumab) Vumerity (diroximel fumarate) Zeposia (ozanimod) **Immunomodulatory Agents NOT to be used Concomitantly** Abrilada (adalimumab-afzb) Actemra (tocilizumab) Adalimumab Adbry (tralokinumab-ldrm) Amjevita (adalimumab-atto) Arcalyst (rilonacept) Avsola (infliximab-axxq) Avtozma (tocilizumab-anoh) Benlysta (belimumab) Bimzelx (bimekizumab-bkzx) Cibinqo (abrocitinib) Cimzia (certolizumab) Cinqair (reslizumab) Cosentyx (secukinumab) Cyltezo (adalimumab-adbm) Dupixent (dupilumab)

Contraindicated as Concomitant Therapy
Ebglyss (lebrikizumab-lbkz)
Enbrel (etanercept)
Entyvio (vedolizumab)
Fasenra (benralizumab)
Hadlima (adalimumab-bwwd)
Hulio (adalimumab-fkjp)
Humira (adalimumab)
Hyrimoz (adalimumab-adaz)
Idacio (adalimumab-aacf)
Ilaris (canakinumab)
Ilumya (tildrakizumab-asmn)
Imuldosa (ustekinumab-srlf)
Inflectra (infliximab-dyyb)
Infliximab
Kevzara (sarilumab)
Kineret (anakinra)
Leqselvi (deuruxolitinib)
Litfulo (ritlecitinib)
Nemluvio (nemolizumab-ilto)
Nucala (mepolizumab)
Olumiant (baricitinib)
Omlyclo (omalizumab-igec)
Omvoh (mirikizumab-mrkz)
Opzelura (ruxolitinib)
Orencia (abatacept)
Otezla (apremilast)
Otulfi (ustekinumab-aauz)
Pyzchiva (ustekinumab-ttwe)
Remicade (infliximab)
Renflexis (infliximab-abda)
Riabni (rituximab-arrx)
Rinvoq (upadacitinib)
Rituxan (rituximab)
Rituxan Hycela (rituximab/hyaluronidase human)
Ruxience (rituximab-pvvr)
Saphnelo (anifrolumab-fnia)
Selarsdi (ustekinumab-aekn)
Siliq (brodalumab)
Simlandi (adalimumab-ryvk)
Simponi (golimumab)
Simponi ARIA (golimumab)
Skyrizi (risankizumab-rzaa)
Sotyktu (deucravacitinib)
Spevigo (spesolimab-sbzo) subcutaneous injection
Stelara (ustekinumab)
Steqeyma (ustekinumab-stba)
Taltz (ixekizumab)
Tezspire (tezepelumab-ekko)
Tofidence (tocilizumab-bavi)
Tremfya (guselkumab)
Truxima (rituximab-abbs)
Tyenne (tocilizumab-aazg)
Tysabri (natalizumab)
Ustekinumab
Velsipity (etrasimod)
Wezlana (ustekinumab-auub)
Xeljanz (tofacitinib)
Xeljanz XR (tofacitinib extended release)
Xolair (omalizumab)
Yesintek (ustekinumab-kfce)
Yuflyma (adalimumab-aaty)
Yusimry (adalimumab-aqvh)

Contraindicated as Concomitant Therapy
Zeposia (ozanimod) Zymfentra (infliximab-dyyb)