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Rituximab Medical Drug Program Summary

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

FDA APPROVED INDICATIONS AND DOSAGE[1-2, 6-7,25]

Agent(s)	Indication(s)	Dosage
Riabni® (rituximab-arrx) Injection for intravenous use	Adult patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin lymphoma (NHL) as a single agent	**Relapsed or refractory, low-grade or follicular, CD20-positiveB-cell NHL:** 375 mg/m^2 IV once weekly for 4 or 8 doses **Retreatment for relapsed or refractory, low-grade or follicular, CD20-positiveB-cell NHL:** 375 mg/m^2 IV once weekly for 4 doses
	Adult patients with 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	**Previously untreated follicular, CD20-positive, B-cell NHL:** Initiation 375 mg/m^{2}IV on day 1 of each chemotherapy cycle for up to 8 doses Maintenance 375mg/m^2 IV as a single agent every 8 weeks for 12 doses
	Adult patients with non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP (cyclophosphamide + vincristine + prednisone) chemotherapy	**Non-progressing, low-grade, CD20-positive, B-cell NHL after first line CVP:** 375 mg/m^2 IV once weekly for 4 doses at 6-month intervals for a maximum of 16 doses
	Adult patients with previously untreated diffuse large B-cell, CD20-positive NHL in combination with (cyclophosphamide, doxorubicin, vincristine, and prednisone) (CHOP) or other anthracycline-based chemotherapy regimens	**Diffuse large B-cell NHL:** 375 mg/m^2 IV on Day 1 of each cycle of chemotherapy for up to 8 infusions

Agent(s)	Indication(s)	Dosage
	Adult patients with previously untreated and previously treated CD20-positive chronic lymphocytic leukemia (CLL) in combination with fludarabine and cyclophosphamide (FC)	**CLL:** 375 mg/m^2 IV the day prior to the initiation of FC chemotherapy, then 500 mg/m^2 on Day 1 of Cycles 2-6 (every 28 days)
	Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids	**GPA and MPA:** **Induction treatment:** 375 mg/m^2 IV once weekly for 4 weeks for patients with active GPA or MPA **Follow up treatment in patients who have achieved disease control with induction treatment:** 500 mg IV every 2 weeks for 2 doses followed by a 500 mg IV infusion every 6 months thereafter based on clinical evaluation
Rituxan® (rituximab) Injection for intravenous use	Adult patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma (NHL) as a single agent	**Relapsed or refectory, low-grade or follicular, CD20-positiveB-cell NHL:** 375 mg/m^2 IV once weekly for 4 or 8 doses **Retreatment for relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL:** 375 mg/m^2 IV once weekly for 4 doses
	Adult patients with 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	**Previously untreated follicular, CD20-positive, B-cell NHL:** Initiation 375 mg/m^{2}IV on day 1 of each chemotherapy cycle for up to 8 doses Maintenance 375mg/m^2 IV as a single agent every 8 weeks for 12 doses
	Adult patients with non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP (cyclophosphamide + vincristine sulfate+ prednisone) chemotherapy	**Non-progressing, low-grade, CD20-positive, B-cell NHL after first line CVP:** 375 mg/m^2 IV once weekly for 4 doses at 6-month intervals for a maximum of 16 doses

Agent(s)	Indication(s)	Dosage
	Adult patients with previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP [cyclophosphamide + doxorubicin hydrochloride (hydroxydaunorubicin) + vincristine sulfate (Oncovin) + prednisone] or other anthracycline-based chemotherapy regimens	**Diffuse large B-cell NHL:** 375 mg/m^2 IV on day 1 of each cycle of chemotherapy for up to 8 infusions
	Adult patients with previously untreated and previously treated CD20-positive chronic lymphocytic leukemia (CLL) in combination with fludarabine and cyclophosphamide (FC)	**CLL:** 375 mg/m^2 IV the day prior to the initiation of FC chemotherapy, then 500 mg/m^2 IV on day 1 of cycles 2-6 (every 28 days)
	Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies	**RA:** Two 1000 mg IV infusions separated by 2 weeks every 24 weeks or based on clinical evaluation, but no sooner than every 16 weeks
	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	**GPA and MPA:** 375 mg/m^2 IV once weekly for 4 weeks in combination with glucocorticoids
	Moderate to severe pemphigus vulgaris (PV) in adult patients	**PV:** Two-1000 mg intravenous infusions separated by 2 weeks in combination with a tapering course of glucocorticoids. Then administer Rituxan as a 500 mg intravenous infusion at Month 12 and every 6 months thereafter or based on clinical evaluation for maintenance treatment **Treatment of relapse:** 1000 mg intravenous infusion on relapse, and consider resuming or increasing the glucocorticoid dose based on clinical evaluation

Agent(s)	Indication(s)	Dosage
Rituxan® Hycela (rituximab and hyaluronidase human) Injection for subcutaneous use		**All indications:** Give full dose of a rituximab product by IV infusion at week 1:
	Adult patients with relapsed or refractory, follicular lymphoma as a single agent	**Relapsed or refractory, follicular lymphoma:** 1400 mg/23400 units subcutaneously (SC) once weekly for 3 or 7 weeks **Retreatment for Relapsed or refractory, follicular lymphoma:** 1400 mg/23400 units SC once weekly for 3 weeks
	Adult patients with 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	**Previously untreated, follicular lymphoma:** Initiation 1400 mg/23400 units SC on day 1 of cycles 2 - 8 (every 21 days) Maintenance if complete or partial response, initiate Rituxan Hycela maintenance at 8 weeks following combination chemotherapy at a dose of 1400 mg/23400 units SC every 8 weeks for 12 doses
	Adult patients with non-progressing (including stable disease), follicular lymphoma as a single agent after first-line CVP (cyclophosphamide + vincristine sulfate+ prednisone) chemotherapy	**Non-progressing, follicular lymphoma after first line CVP chemotherapy:** 1400 mg/23400 units SC once weekly for 3 weeks at 6 month intervals for a maximum of 16 doses
	Adult patients with previously untreated diffuse large B-cell lymphoma in combination with CHOP (cyclophosphamide + doxorubicin hydrochloride + vincristine sulfate + prednisone) or other anthracycline-based chemotherapy regimens	**Diffuse large B-cell NHL:** 1400 mg/23400 units SC on day 1 of cycles 2 – 8 of CHOP chemotherapy for up to 7 cycles
	Adult patients with chronic Lymphocytic Leukemia (CLL) in combination with fludarabine and cyclophosphamide (FC)	**CLL:** 1600 mg/26800 units SC on day 1 of cycles 2 – 6 (every 28 days) for a total of 5 cycles

Agent(s)	Indication(s)	Dosage
	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 relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin lymphoma (NHL) as a single agent	**Relapsed or refectory, low-grade or follicular, CD20-positiveB-cell NHL:** 375 mg/m^2 IV once weekly for 4 doses
	Adult patients with 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	**Previously untreated follicular, CD20-positive, B-cell NHL:** Initiation 375 mg/m^2IV on day 1 of each chemotherapy cycle for up to 8 doses Maintenance 375mg/m^2 IV as a single agent every 8 weeks for 12 doses
	Adult patients with non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP (cyclophosphamide + vincristine + prednisone) chemotherapy	**Non-progressing, low-grade, CD20-positive, B-cell NHL after first line CVP:** 375 mg/m^2 IV once weekly for 4 doses at 6-month intervals for a maximum of 16 doses
	Adult patients with previously untreated diffuse large B-cell, CD20-positive NHL in combination with (cyclophosphamide, doxorubicin, vincristine, and prednisone) (CHOP) or other anthracycline-based chemotherapy regimens	**Diffuse large B-cell NHL:** 375 mg/m^2 IV on Day 1 of each cycle of chemotherapy for up to 8 infusions
	Adult patients with previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC)	**CLL:** 375 mg/m^2 IV the day prior to the initiation of FC chemotherapy, then 500 mg/m^2 on Day 1 of Cycles 2-6 (every 28 days)
	Treatment of granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis and microscopic polyangiitis (MPA) in adult patients in	**GPA and MPA:** **Induction treatment:** 375 mg/m^2 IV once weekly for 4 weeks for patients with active GPA or MPA

Agent(s)	Indication(s)	Dosage
	combination with glucocorticoids	**Follow up treatment in patients who have achieved disease control with induction treatment:** 500 mg IV every 2 weeks for 2 doses followed by 500 mg IV infusion every 6 months thereafter based on clinical evaluation
Truxima® (rituximab-abbs) Injection for intravenous use	Adult patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma (NHL) as a single agent	**Relapsed or refectory, low-grade or follicular, CD20-positiveB-cell NHL:** 375 mg/m^2 IV once weekly for 4 doses
	Adult patients with 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	**Previously untreated follicular, CD20-positive, B-cell NHL:** Initiation 375 mg/m^2IV on day 1 of each chemotherapy cycle for up to 8 doses Maintenance 375mg/m^2 IV as a single agent every 8 weeks for 12 doses
	Adult patients with non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP (cyclophosphamide + vincristine + prednisone) chemotherapy	**Non-progressing, low-grade, CD20-positive, B-cell NHL after first line CVP:** 375 mg/m^2 IV once weekly for 4 doses at 6-month intervals for a maximum of 16 doses
	Adult patients with previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or other anthracycline-based chemotherapy regimens	**Diffuse large B-cell NHL:** 375 mg/m^2 IV on Day 1 of each cycle of chemotherapy for up to 8 infusions
	Adult patients with previously untreated and previously treated CD20-positive chronic lymphocytic leukemia (CLL) in combination with fludarabine and cyclophosphamide (FC)	**CLL:** 375 mg/m^2 IV the day prior to the initiation of FC chemotherapy, then 500 mg/m^2 on Day 1 of Cycles 2-6 (every 28 days)
	Rheumatoid arthritis (RA) in combination with methotrexate in adult patients	**RA:** Two 1000 mg intravenous infusions separated by 2

Agent(s)	Indication(s)	Dosage
	with moderately-to-severely-active RA who have had inadequate response to one or more TNF antagonist therapies	weeks every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks
	Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids	**GPA and MPA: Induction treatment:** 375 mg/m^2 IV once weekly for 4 weeks for patients with active GPA or MPA **Follow up treatment in patients who have achieved disease control with induction treatment:** 500 mg IV every 2 weeks for 2 doses followed by 500 mg IV every 6 months thereafter based on clinical evaluation

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. The National Cancer Institute estimates that in 2019 there will be 74,200 new cases of NHL and 19,970 deaths from NHL in the United States. 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]

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. It accounts for 1 out of every 3 cases. Treatment for B-cell NHL includes radiation therapy, immunotherapy with rituximab, systemic chemotherapy, or combinations of these therapies.[3]

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]

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]

Efficacy[1-2]
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.

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.

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.

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.

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 ($p<0.0001$). 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.

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 (hydroxydanorubicin) + 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.

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.

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.

Safety[1-2,6-7,25]
Riabni (rituximab-arrx), **Rituxan** (rituximab) contains 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.

Rituxan has no labeled contraindications, but does contain warnings for tumor lysis syndrome, infections, cardiac arrhythmias and angina, bowel obstruction and perforation, cytopenias. In addition, do not administer live virus vaccines prior to or during Rituxan therapy.

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.

Monitor patients for tumor lysis syndrome, PML, hepatitis B reactivation, infections, cardiac arrhythmias and angina, bowel obstruction and perforation.

Rituxan Hycela has no labeled contraindications, but does contain warnings for hypersensitivity, tumor lysis syndrome, cardiac adverse reactions, renal toxicity, bowel obstruction and perforation, embryo-fetal toxicity. In addition, live virus vaccines are not recommended to be given prior to or during treatment with Rituxan Hycela.

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.

Clinical Rationale 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 decreasing inflammation, relieve symptoms, prevent joint and organ damage, improve physical function/overall well-being, and reduce long term complications.[11,25] 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.[11]

American College of Rheumatology (ACR) guidelines recommend a treat-to-target approach in therapy, regardless of disease activity. Treatment goals are for low disease activity or remission. ACR guidelines categorize therapy for those with early RA (disease duration <6 months) or established RA (disease duration ≥6 months) as follows:[11]

- In general, MTX is preferred initial DMARD therapy for most patients with RA with active disease.
- For early RA patients, the ACR recommends the following:

    - Naïve to therapy, DMARDs, methotrexate (MTX) preferred, as initial, monotherapy therapy unless contraindicated. Other DMARD monotherapy options include sulfasalazine, hydroxychloroquine, and leflunomide.
    - Moderate or high disease activity despite DMARD monotherapy: treatment with combination DMARDs or a TNF-inhibitor (adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab) or a non-TNF inhibitor (abatacept, rituximab, or tocilizumab [excludes anakinra]), with or without MTX.
    - Moderate or high disease activity despite the previous DMARD or biologic therapy, addition of low-dose glucocorticoid (≤10 mg/day of prednisone or equivalent) to bridge therapy until therapeutic effects of DMARD is reached. ACR also recommends short-term (< 3 months) with lowest dose of glucocorticoids for flares.
- For established RA patients, the ACR recommends the following:
    - Low disease activity and is DMARD naïve, DMARD monotherapy, MTX preferred, is recommended over a TNF-inhibitor.
    - Moderate or high disease and is DMARD naïve: DMARD monotherapy, MTX preferred, is recommended over double or triple DMARD therapy and tofacitinib.
    - Moderate-high disease activity despite DMARD monotherapy: combination DMARD therapy OR the addition of TNF inhibitor, non-TNF biologic, or tofacitinib with or without MTX is recommended rather than continuing DMARD monotherapy. Combination biologic therapy and MTX is recommended over biologic monotherapy.
    - Moderate or high disease despite TNF-inhibitor and not on DMARD: addition of one or two DMARD, rather than TNF-inhibitor monotherapy

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.[26-28] 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.[27-28] 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.[11]

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 to 6 months with non-biologic triple therapy following an inadequate response to MTX therapy.[11,28]

Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis

Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) are classified as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides because most patients with generalized disease have antibodies against proteinase 3 or myeloperoxidase. B lymphocytes play an important role in the pathogenesis of autoimmune diseases, including ANCA-associated vasculitis. The ANCA-associated vasculitides affect small-to-medium-size blood vessels, with a predilection for the respiratory tract and kidneys. Prevalence of GPA in the U.S. is estimated to be 3 cases per 100,000 people. A high percentage of patients experience permanent damage including end-stage renal disease, chronic pulmonary dysfunction, hearing loss, destructive sinus disease, saddle nose deformities, perforation of the nasal septum, proptosis, and blindness[6]

Cyclophosphamide or rituximab in combination with glucocorticoids are usually used for initial immunosuppressive therapy. Some studies have described the use of both cyclophosphamide and rituximab for initial therapy although this approach is controversial.[9]

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.[24]

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.[24]

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).[24]

Efficacy[1]
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.

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.

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.

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.

Safety[1]
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.

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.

Riabni (rituximab-arrx), **Rituxan** (rituximab), **Rituxan Hycela** (rituximab and hyaluronidase human), **Ruxience** (rituximab-pvvr), and **Truxima** (rituximab-abbs) do not have any FDA labeled contraindications.

Compendia Supported Indications
For the purposes of the 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.

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]

The American Academy of Neurology has recommended alemtuzumab, fingolimod, and natalizumab as options for patients with MS with highly active MS. Sub-analysis from phase III pivotal trials showed alemtuzumab, fingolimod, and natalizumab resulted in more favorable outcomes (reduction in relapses and MRI measures) in the patients with highly active MS compared to interferon-β therapy.[11] Based on available evidence, clinicians agree that newly diagnosed patients with MS, who have clinical and radiographic markers of poor prognosis in the early stages of MS, should be treated with agents with higher efficacy from the onset, even if associated with greater risks. There lacks a consensus for what constitutes as very active MS, however.[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]

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]

Neuromyelitis Optica Spectrum Disorder
Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease associated with central nervous system (CNS) inflammation, primarily in the optic nerves (optic neuritis) and spinal cord (acute transverse myelitis).[19,20] Symptoms of NMOSD include temporary vision loss, pain, weakness in the extremities, bladder and bowel incontinence, and nausea and vomiting. In most cases, symptoms of NMOSD will relapse and remit over time similarly to certain forms of multiple sclerosis (MS), but the two are pathologically distinct and should be treated with different disease-modifying drugs. Due to similarities in the way that NMOSD and MS frequently present, it is critical to distinguish between the two. Compared to MS, the optic neuritis and myelitis associated with NMOSD tend to be more severe and the

brain MRI is more commonly normal; additionally, spinal fluid analysis does not typically show oligoclonal bands in NMOSD.

NMOSD can be classified as AQP4 antibody positive or negative. The diagnostic criteria for NMOSD with AQP4 positive diagnosis are a positive test for AQP4-IgG, exclusion of alternative diagnoses, and at least one of the following core characteristics[21]:

1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome (episodes of otherwise unexplained hiccups or nausea and vomiting)
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

An international consensus panel reached several conclusions in addition to the above criteria to establish a diagnosis of NMOSD. First, at least 1 discrete clinical attack of CNS symptoms must occur to establish a diagnosis of NMOSD. 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.[21]

Disability in NMOSD is a direct consequence of the relapse. Spontaneous gradual progression of disability like in MS is very rare in NMOSD. Thus, NMOSD 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]

Rituximab is a mouse and human chimeric IgG1 monoclonal antibody that binds to CD20 B-lymphocyte surface antigen, which is involved in B-cell activation, differentiation, and growth. Studies have shown the efficacy of rituximab in treating autoimmune diseases, and the drug has been increasingly administered to patients with refractory or severe NMOSD. A systematic review from 2016 evaluated 46 studies assessing 2 primary outcome measures (differences in the ARR ratio and the mean EDSS score) before and after rituximab therapy.

The combined data sets of all studies included a total of 438 patients treated with rituximab. In 57 patients rituximab was used as a first line therapy, 124 patients were treated with immunomodulatory drugs before rituximab, 143 patients were receiving immunosuppressive drugs at the time of the first infusion of rituximab, and 58 patients had plasma exchange or IVIG before rituximab therapy.[23]

The efficacy outcome measures were pooled using the method of inverse variance, with random effects on the logit-transformed proportions. The combined estimates were reported with 95% Cis. The rituximab regimen was available for 313 patients and varied among the studies. 139 patients received 375 mg/m^2 weekly for 4 weeks, 156 patients were treated with 1 g every 2 weeks for 2 times, 9 patients received 500 mg weekly for 2 weeks, and 9 patients used different therapeutic regimens.[23]

The mean (SE) reduction in the mean ARR ratio after rituximab therapy was 0.79. No significant correlation was detected between the outcome of ARR ratio change and the following variables:[23]

- Mean number of rituximab reinfusions
- Immunomodulatory drugs before rituximab
- IVIG
- Plasma exchange
- Different rituximab regimens
- Disease duration
- AQP4-IgG serostatus

The EDSS score was reported in 18 studies included in the meta-analysis. Rituximab treatment resulted in a mean (SE) reduction in the mean EDSS score by 0.64. A significant correlation was observed between disease duration and the EDSS score (p = 0.04; 95% CI). No significant correlation was observed between the standardized mean difference of the EDSS score and the following variables:[23]

- Mean number of rituximab reinfusions
- Immunomodulatory drugs before rituximab
- IVIG
- Plasma exchange
- Different rituximab regimens
- AQP4-IgG serostatus

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Rituximab Oncology Medical Drug Criteria

TARGET AGENT(S)
Riabni® (rituximab-arrx)
Rituxan® (rituximab)
Rituxan® Hycela (rituximab and hyaluronidase human)

Preferred Agent(s)	Non-Preferred Agent(s)
Ruxience (rituximab-pvvr) Truxima (rituximab-abbs)	Riabni (rituximab-arrx) Rituxan (rituximab) Rituxan Hycela (rituximab and hyaluronidase human)

Brand (generic)	GPI	HCPCS code	Multisource code
Riabni (rituximab-arrx)			
100 mg/10 mL single dose vial	21351860142020	Q5123	M, N, O, or Y
500 mg/50 mL single dose vial	21351860142040	Q5123	M, N, O, or Y
Rituxan (rituximab)			
100 mg/10 mL single dose vial	21351860002020	J9312	M, N, O, or Y
500 mg/50 mL single dose vial	21351860002040	J9312	M, N, O, or Y
Rituxan Hycela (rituximab and hyaluronidase human)			
1400 mg/23400 units per 11.7 mL vial	21990002642020	J9311	M, N, O, or Y
1600 mg/26800 units per 13.4 mL vial	21990002642040	J9311	M, N, O, or Y

CRITERIA FOR APPROVAL
Oncology Evaluation
Target Agent(s) will be approved for oncologic uses when ALL of the 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:
      i. The requested agent will be used as a single agent
      OR
      ii. 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:
      i. The requested agent will be used for initial therapy AND the requested agent will be used in combination with first line chemotherapy
      OR

ii. 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

iii. 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:
    i. BOTH of the following:
        a. The requested agent will be used after first-line CVP (cyclophosphamide/Cytoxan, vincristine/Oncovin, prednisone) chemotherapy
        AND
        b. The requested agent will be used as a single agent

    OR

    ii. 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:
    i. The requested agent will be used in combination with CHOP [cyclophosphamide + doxorubicin hydrochloride (hydroxydaunorubicin) + vincristine sulfate (Oncovin) + prednisone] regimen
    OR
    ii. The requested agent will be used in another anthracycline-based chemotherapy regimen
    OR
    iii. 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 the diagnosis of CD20-positive Chronic lymphocytic leukemia (CLL) AND ONE of the following:
    i. The requested agent will be used in combination with fludarabine and cyclophosphamide (FC)
    OR
    ii. 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 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

G. 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. ONE of the following:
   A. The patient's age is within the FDA labeling for the requested indication for the requested agent

   OR

   B. The prescriber has provided information in support of using the requested agent for the patient's age

AND

4. ONE of the following:
   A. The requested agent is a preferred agent (listed below)

   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 that is NOT expected to occur with the requested agent (medical records required)

Preferred Agent(s)
Ruxience (rituximab-pvvr) Truxima (rituximab-abbs)

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 NCCN 1 or 2A compendia supported dosing for the requested indication

   OR

   B. The prescriber has provided information in support of the higher dose for the requested indication

Length of Approval: 12 months or for duration of treatment as supported in FDA labeling or compendia, whichever is shorter.

Compendia Allowed: NCCN 1 or 2a recommended use

Rituximab Non-Oncology Medical Drug Criteria

TARGET AGENT(S)
Riabni® (rituximab-arrx)
Rituxan® (rituximab)

Preferred Agent(s)	Non-Preferred Agent(s)
Ruxience (rituximab-pvvr) Truxima (rituximab-abbs)	Riabni (rituximab-arrx) Rituxan (rituximab)

Brand (generic)	GPI	HCPCS code	Multisource code
Riabni (rituximab-arrx)			
100 mg/10 mL single dose vial	21351860142020	Q5123	M, N, O, or Y
500 mg/50 mL single dose vial	21351860142040	Q5123	M, N, O, or Y
Rituxan (rituximab)			
100 mg/10 mL single dose vial	21351860002020	J9312	M, N, O, or Y
500 mg/50 mL single dose vial	21351860002040	J9312	M, N, O, or Y

CRITERIA FOR APPROVAL
Non-Oncology Initial Evaluation
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. ONE of the following:
      i. The patient has a diagnosis of moderate to severely active rheumatoid arthritis (RA) AND BOTH of the following:
         1. ONE of the following:
            a. The patient has had an inadequate response to maximally tolerated methotrexate (e.g., titrated to 25 mg weekly) for at least 3-months
               OR
            b. The patient has had an inadequate response to another conventional agent (e.g., hydroxychloroquine, leflunomide, or sulfasalazine) used in the treatment of RA for at least 3-months
               OR
            c. The patient has an intolerance or hypersensitivity to ALL conventional agents (i.e., methotrexate, hydroxychloroquine, leflunomide, and 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, and sulfasalazine) used in the treatment of RA

OR

e. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA indicated for RA

AND

2. ONE of the following:
    a. The patient has tried and had an inadequate response to at least one biologic immunomodulator FDA indicated for RA for at least 3 months

    OR

    b. The patient has an intolerance or hypersensitivity to ALL biologic immunomodulators indicated for RA

    OR

    c. The patient has an FDA labeled contraindication to ALL biologic immunomodulators indicated for RA

OR

ii. The patient has a diagnosis of granulomatosis with polyangiitis (GPA) [Wegener's granulomatosis] OR Microscopic polyangiitis (MPA) AND ONE of the following:
    1. The patient will be using a corticosteroid in combination with the requested agent

    OR

    2. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to at least one corticosteroid

OR

iii. The patient has a diagnosis of myasthenia gravis AND ONE of the following:
    1. The patient failed treatment with azathioprine

    OR

    2. The patient has an intolerance or hypersensitivity to azathioprine

    OR

    3. The patient has an FDA labeled contraindication to azathioprine

OR

iv. The patient has a diagnosis of post-transplant lymphoproliferative disorder

OR

v. The patient has a diagnosis of moderate to severe pemphigus vulgaris (PV)

OR

vi. The patient has a diagnosis of relapsing form of multiple sclerosis (MS) AND BOTH of the following:
    1. ONE of the following:
        a. The patient has highly active MS disease activity AND BOTH of the following:
            i. The patient has ≥ 2 relapses in the previous year

            AND

            ii. ONE of the following:
                1. The patient has ≥1 gadolinium enhancing lesion on MRI

                OR

2. The patient has a significant increase in T2 lesion load compared with a previous MRI

OR

b. The patient has tried and had an inadequate response to ONE preferred agent for the treatment of relapsing forms of MS

OR

c. The patient has an intolerance or hypersensitivity to ALL preferred agents for the treatment of relapsing forms of MS

OR

d. The patient has an FDA labeled contraindication to ALL preferred agents for the treatment of relapsing forms of MS

AND

2. The patient will NOT be using the requested agent in combination with an additional disease modifying agent (DMA) for the requested indication

OR

vii. The patient has a diagnosis of primary progressive form of multiple sclerosis

OR

viii. 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

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, or Uplizna for the requested indication

OR

ix. The patient has another FDA labeled indication for the requested agent

OR

x. The patient has an indication supported by compendia for the requested agent

AND

3. ONE of the following:
   A. The requested agent is a preferred agent (listed below)
      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)

Preferred Agent(s)
Ruxience (rituximab-pvvr)
Truxima (rituximab-abbs)

AND

4. ONE of the following:
   A. The patient's age is within FDA labeling for the requested agent for the requested agent
      OR
   B. The prescriber has provided information in support of using the requested agent for the patient's age

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 will NOT be using the requested agent with another biologic immunomodulator agent or Otezla for the requested indication

AND

8. The patient has been screened for hepatitis B infection measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc)

AND

9. If the patient is positive for hepatitis B, then the patient has begun hepatitis B therapy

AND

10. 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. The prescriber has provided information in support of therapy with a higher dose for the requested indication

Length of Approval: 1 month for refractory myasthenia gravis
12 months for all other diagnoses

Compendia Allowed: AHFS, or DrugDex 1 or 2a level of evidence

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
   AND
2. 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
3. ONE of the following:
   A. The requested agent is a preferred agent (listed below)
      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)

Preferred Agent(s)
Ruxience (rituximab-pvvr) Truxima (rituximab-abbs)

   AND
4. 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
5. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
6. The patient will NOT be using the requested agent in combination with another biologic immunomodulator or Otezla for the requested indication
   AND
7. If the requested indication is a relapsing form of multiple sclerosis (MS): the patient will NOT be using the requested agent with an additional disease modifying agent (DMA) for the requested indication
   AND
8. If the requested indication is neuromyelitis optica spectrum disorder (NMOSD), the patient will not be using the requested agent in combination with Enspryng, Soliris, or Uplizna
   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. The prescriber has provided information in support of therapy with a higher dose for the requested indication

Length of Approval: Up to 12 months

