in patients with severe ANCA-associated vasculitis showed that a single course of Rituxan was noninferior to cyclophosphamide followed by maintenance with azathioprine at Month 12 and 18.[25]

Dosing in ANCA-Associated Vasculitis. *Dosing must meet the following:* 375 mg/m^2 IV once weekly.[1,7,9]

The approved dose for MPA and GPA (375 mg/m^2 once weekly for 4 weeks) is the dose most often evaluated in the literature for ANCA-associated vasculitis. However, other doses (e.g., 500 mg on Days 1 and 15) have also demonstrated some efficacy. Alternate doses will be evaluated on a case-by-case basis.[28]

Initial Approval/Extended Approval.[1,9-10]

- **A)** *Initial Approval*. Initial approval is for 4 weeks of therapy.
- **B)** *Extended Approval*. Approve for 1 year if the patient has responded to therapy, as determined by the prescribing physician.[10]

EULAR/ERA-EDTA recommendations for ANCA-associated vasculitis mention Rituxan in combination with low-dose corticosteroids as a potential treatment option for remission-maintance therapy. Remission-maintenance therapy is recommended for at least 24 months following induction of sustained remission.[7] Rituxan has also been successfully utilized to retreat patients with ANCA-associated vasculitides when a minimum of 6 months has elapsed since the first course of Rituxan.[10] Relapse occurred in 57% of patients who achieved complete remission following initial treatment with Rituxan with a median time to relapse of 11.5 months. Of the patients who received a second course of Rituxan, 84% of patients (n = 32/38) experienced a second complete remission or maintained remission. Patients were allowed to receive additional repeat courses with a maximum of seven courses of Rituxan reported.

Duration of Therapy in ANCA-Associated Vasculitis.[9-10] EULAR/ERA-EDTA guidelines recommend that remission-maintenance therapy be continued for at least 24 months following induction of sustained remission.[7] Patients may be retreated, based on the opinion of the prescribing physician.

Labs/Diagnostics. None required.

2. Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL).

Criteria. *The patient must meet the following criteria (A AND B)*:[1,11]

- **A)** Rituxan is prescribed by or in consultation with an oncologist; AND
- **B)** The patient has CD20-positive disease.

Rituxan is indicated in combination with fludarabine and cyclophosphamide for treatment of patients with previously untreated and previously treated CD20-positive CLL.[1] The National Comprehensive Cancer Network (NCCN) guidelines for CLL/SLL (version 2/2018) note that Rituxan is recommended as monotherapy or in multiple combination regimens as a first-line therapy or relapsed/refractory therapy in a variety of clinical situations for patients with CLL or SLL.[6,36] SLL is considered to be different manifestations of the same disease as CLL and is managed similarly.[11,36]

Dosing in CLL/SLL. *Dosing must meet ONE of the following (A OR B):*[1,11]

A. 375 mg/m^2 as an IV infusion, then 500 mg/m^2 on Day 1 of Cycles 2 through 6; OR

i. B. 375 mg/m^2 as an IV infusion on Day 1 of each chemotherapy cycle.

Rituxan has been included in various treatment regimens using various doses for CLL.[1,11] The NCCN guidelines also mention Rituxan for maintenance of CLL.

Note: Other dosing schedules will be evaluated on a case-by-case basis for clinical appropriateness.

Initial Approval/Extended Approval.

A) *Initial (or Retreatment) Approval*: Up to 8 doses.[1,11]

Extended Approval: Extended dosing will be evaluated on a case-by-case basis for clinical appropriateness.

Duration of Therapy in CLL/SLL.[1,11] Duration of treatment is usually for six to eight doses. Note: Extended treatment will be evaluated on a case-by-case basis for clinical appropriateness.

Labs/Diagnostics.

None required.

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3. B-Cell Lymphoma (e.g., Follicular Lymphoma, Diffuse Large B-Cell Lymphoma [DLBCL], Acquired Immune Deficiency [AIDS]-Related B-Cell Lymphoma, Burkitt Lymphoma, Castleman's Disease, Marginal Zone Lymphoma [e.g., extranodal or MALT {gastric or nongastric}, nodal, or splenic marginal zone lymphoma], Mantle Cell Lymphoma, Post-Transplant Lymphoproliferative Disorders, Gray Zone Lymphoma).

Criteria. *The patient must meet the following criterion (*:[1,11]

Rituxan is prescribed by or in consultation with an oncologist or hematologist

Rituxan is indicated for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent; for previously untreated follicular, CD-positive, B-cell NHL in combination with first-line chemotherapy and, in patients achieving a complete or partial response to Rituxan in combination with chemotherapy, as single-agent maintenance therapy; for nonprogressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line treatment with CVP chemotherapy; and in previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens.[1] Rituxan is appropriate in many clinical situations and features prominently in NHL treatment guidelines.

NCCN guidelines for B-cell lymphomas (version 6.2017) list Rituxan as a first-line, second-line, and/or suggested treatment regimen in clinical situations for CD20-positive NHL variants (e.g., patients with acquired immunodeficiency syndrome [AIDS]-related B-cell lymphoma [for example, certain patients with Burkitt lymphoma, diffuse large B-cell lymphoma, lymphoma associated with Castleman's disease, primary effusion lymphoma], follicular lymphoma, gastric MALT lymphoma, mantle cell lymphoma, nongastric MALT lymphoma, and post-transplant lymphoproliferative disorder).[5] Rituxan is also recommended in certain patients with hairy cell leukemia for relapse or refractory disease. T-cell NHLs (e.g., mycosis fungoides, anaplastic large cell lymphoma, and precursor T-lymphoblastic lymphoma) are treated with other therapies. Grey zone lymphomas are a group of lymphomas with overlapping

histological and clinical features of different lymphoma subtypes. Grey zone lymphomas appear to have a worse prognosis and no standard of care or consensus exists for management; however, aggressive, large B-cell lymphoma regimens have been proposed and Rituxan + chemotherapy should be considered if the tumor expresses CD20.

Dosing in B-Cell Lymphoma. *Dosing must meet ONE of the following (A OR B):*[1,5]

A) Initial Treatment or Retreatment: Dose must meet ONE of the following:
- **i.** 375 mg/m^2 as an intravenous infusion given once weekly; OR
- **ii.** 375 mg/m^2 as an IV infusion on Day 1 of each chemotherapy cycle; OR
- **iii.** If administered with Zevalin: 250 mg/m^2 as an IV infusion on Day 1 and then repeat the dose on Day 7, 8, or 9.

B) Maintenance Treatment: Patient must meet ONE of the following:
- **i.** 375 mg/m^2 as an IV infusion every 8 weeks[1-2]; OR
- **ii.** 375 mg/m^2 as an IV infusion every 12 weeks[2];
- **iii.** 375 mg/m^2 as an IV infusion once weekly for 4 weeks (repeated at 6-month intervals)[1]; OR
- **iv.** 375 mg/m^2 as an IV infusion once weekly repeated monthly.[13-14]

The dosing schedule of Rituxan varies, depending on the type of B-Cell Lymphoma.[1,11] Most patients will receive up to eight doses of Rituxan for treatment of NHL.
Note: Other dosing schedules have been evaluated in the literature and will be evaluated on a case-by-case basis for clinical appropriateness.

Initial Approval/Extended Approval.

A) *Initial (or Retreatment) Approval*: Approve up to 8 doses.[1] If used with Zevalin, approve two doses of Rituxan which is required to complete the treatment course.

B) *Extended Approval*: Approve at additional 6-month intervals if the patient requires additional treatment, as determined by the prescribing physician.

NCCN guidelines note that Rituxan is used for maintenance therapy in a variety of situations, including with autologous stem cell rescue and is also included in multiple regimens for second-line and subsequent therapy (e.g., as part of concurrent and sequential chemoimmunotherapy regimens).

Duration of Therapy in NHL.[1] Duration of treatment is for four to eight doses unless administered with Zevalin when the duration of treatment is two doses (which are generally separated by 7 to 9 days).
Maintenance Therapy. Some patients will continue on Rituxan for maintenance therapy based on the opinion of the prescribing physician.

Labs/Diagnostics. None required.

4. Rheumatoid Arthritis (RA).

Criteria. *Patient must meet the following criteria (A AND B)*:[1-2]

A) The patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months (e.g., methotrexate [oral or injectable], leflunomide, hydroxychloroquine, and sulfasalazine).
(NOTE: An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already has a 3-month trial at least one biologic disease-modifying antirheumatic drug (DMARD) [e.g., Cimzia, Humira, Remicade, Simponi {Aria or SC}, Actemra {IV or SC}, Kineret, Orencia {IV or SC}, and Rituxan]. These patients who have already tried a biologic for RA are not required to "step back" and try a conventional synthetic DMARD); AND

B) Rituxan is prescribed by or in consultation with a rheumatologist.

Rituxan in combination with MTX is indicated for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to one or more TNF antagonist therapies.[1] Guidelines from the American College of Rheumatology (ACR) [2015] have TNF inhibitors (e.g., Cimzia, Enbrel, Humira, Remicade, Simponi SC/Aria) and non-TNF biologics (i.e., Actemra, Orencia, Rituxan), administered with or without MTX, equally positioned as a recommended therapy following a trial of a conventional synthetic DMARD (e.g., MTX, leflunomide, hydroxychloroquine, sulfasalazine).[2] The dose of Rituxan for RA is two-1,000 mg IV infusions separated by 2 weeks (one course) every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks.[1]

Dosing in RA in an Adult. *Dosing must meet ONE of the following (A OR B):*[1-2,16]

A) Two 1,000-mg IV infusions separated by 2 weeks; OR

B) Two 500-mg IV infusions separated by 2 weeks.

The approved dose of Rituxan in RA is two 1,000-mg doses separated by 2 weeks; however, two 500-mg doses have also been used and provide a relatively equivalent clinical response.[2] The higher dose is associated with an earlier response, higher degrees of clinical response, and less radiographic progression compared to the lower dose.

Initial Approval/Extended Approval.

A) *Initial Approval*: Initial approval is for 4 months which is an adequate duration for the patient to receive two doses of Rituxan.

B) *Extended Approval*:

- **i.** Following one course of therapy, approve an additional 4 months (which is an adequate duration to receive an additional two doses of Rituxan) if the patient meets BOTH of the following conditions (a and b):
  - **a)** At least 16 weeks will elapse between courses of Rituxan (i.e., at least 16 weeks will elapse between the first dose of the previous Rituxan regimen and the first dose of the repeat course); and
  - **b)** The patient requires an additional course of therapy, as determined by the prescribing physician.
- **ii.** Following two or more courses of therapy, approve for 1 year if the patient meets BOTH of the following conditions (a and b):

a) According to the prescribing physician, at least 16 weeks will elapse between courses of Rituxan (i.e., at least 16 weeks will elapse between the first dose of the previous Rituxan regimen and the first dose of the repeat course); AND
b) The patient has responded to therapy (e.g., less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids), as determined by the prescribing physician.

Repeated treatment courses are effective in patients who respond to therapy, and additional courses in a patient with a partial response can lead to an improved response.[9] Subsequent courses should be administered every 24 weeks based on a clinical evaluation, but not before 16 weeks have elapsed.[1] Some patients who do not respond to the initial course will respond to a second course of treatment.[9,16] Retreatment in patients with a partial response at Month 6 may lead to an additional response at Week 48.[9]

Duration of Therapy in RA in an Adult. Indefinite if the patient is responding.[9]

Labs/Diagnostics. None required.

Other Uses with Supportive Evidence
5. <u>Graft-Versus-Host Disease (GVHD)</u>.

Criteria. *<u>Patient must meet the following criteria (A AND B)</u>*:
A) Rituxan is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center; AND
B) The patient meets ONE of the following conditions (i <u>or</u> ii):
i. The patient has tried one immunosuppressant for graft-versus-host disease (GVHD) [e.g., one corticosteroid such as methylprednisolone, antithymocyte globulin, cyclosporine, Thalomid® {thalidomide tablets}, tacrolimus, mycophenolate mofetil, sirolimus {Rapamune®, generic}, Nipent® {pentostatin infusion}, imatinib {Gleevec®, generic}, methotrexate, or infliximab {e.g., Remicade, Inflectra}]; OR
ii. The patient is concurrently receiving at least one of these medications (e.g., one corticosteroid such as methylprednisolone, antithymocyte globulin, cyclosporine, Thalomid, tacrolimus, mycophenolate mofetil, sirolimus, Nipent, imatinib, or methotrexate) in combination with Rituxan.

Guidelines from the British Committee for Standards in Heamatology (BCSH) and the British Society for Bone Marrow Transplant have recommendations for the management of chronic GVHD (2012).[29] Corticosteroids (e.g., starting dose of prednisone 1 mg/kg) are recommended as first-line treatment for chronic GVHD. Calcineurin inhibitors (e.g., cyclosporine, tacrolimus) are noted to have utility as steroid-sparing agents. Patients with steroid-refractory chronic GVHD are treated with based on organ involvement and toxicity profile. Rituxan is listed as a potential second-line treatment for patients with refractory cutaneous or musculoskeletal chronic GVHD or third-line for treatment of GVHD involving other organs. Other second-line treatments include extracorporeal photopheresis (ECP) for skin, oral, or

liver chronic GVHD; mammalian target of rapamycin (mTOR) inhibitors (e.g., sirolimus [Rapamune®, generic]) or pentostatin for refractory chronic GVHD; and imatinib (Gleevec®, generic) for refractory pulmonary or sclerodermatous chronic GVHD. ECP and imatinib are also listed as potential third-line agents for treatment of chronic GVHD involving other organs. Other third-line agents for refractory GVHD are mycophenolate mofetil, MTX, and pulsed corticosteroids.

Rituxan has also been evaluated as initial therapy in patients with chronic GVHD. A prospective, Phase II study enrolled 25 patients with a first episode of symptomatic extensive chronic GVHD that required systemic immunosuppression.[31] Organ involvement was oral (n = 24), cutaneous (n = 14), gastrointestinal (n = 12), ocular (n = 10), hepatic (n = 8), genital (n = 5), pulmonary (n = 2), and musculoskeletal (n = 1). All patients were started on Rituxan 375 mg/m2 on Days 1, 8, 15, and 22, then one dose every 3 months for 4 doses. In all patients, tacrolimus or sirolimus was given throughout the study. Mycophenolate mofetil was given at a dose of 15 mg/kg BID. Locally acting corticosteroids and/or topical agents were permitted. Systemic corticosteroids were allowed, at the discretion of the treating physician, if chronic GVHD progressed after 2 weeks of therapy or showed no improvement after 4 weeks of therapy. However, patients requiring > 4 weeks of systemic corticosteroids and those requiring additional immunosuppressants were considered treatment failures. All patients were followed through Year 2. Clinical response was noted in 22 out of 25 patients. Of the 22 responders, median time to maximum response was 161 days (range, 35 to 300 days). Overall response rate was 88% (n = 22/25) and compete response rate was 84% (n = 21/25). In all, 80% of patients (n = 20/25) did not receive corticosteroids during the study. With a median follow-up of 27 months for surviving patients, the estimated 2-year overall survival is 82%.

Dosing in GVHD. *Dosing must meet the following (A, B, OR C):*[30-31,35]

- **A)** 375 mg/m^2 IV once weekly; OR
- **B)** 375 mg/m^2 IV once weekly for 4 doses followed by a similar infusion once monthly or once every 3 months; OR
- **C)** 50 mg/m^2 once weekly.

Use of Rituxan in GVHD has been evaluated in retrospective case reviews and non-controlled prospective studies.[30] In most cases, the dose used was 375 mg/m^2. In Phase II studies, patients have received similar doses at 1-month or 3-month intervals.[31,35] There is also a small retrospective study (n = 13) which reported overall response rates of 50% to 75% with use of Rituxan 50 mg/m^2 once weekly in patients with skin, oral mucosa, or muscular involvement.[30]

Initial Approval/Extended Approval.

- **A)** *Initial Approval*. Approve for 1 month (which is up to 4 doses of therapy, if needed).
- **B)** *Extended Approval*. Approve in 6-month intervals if the patient has responded, as determined by the prescribing physician. Patients with GVHD are monitored closely and should have a response within the first months of treatment. The patient may not have a full response by the end of Month 1, but there should be some response.

In most of the retrospective case reviews and non-controlled studies, one cycle (defined as 3 or 4 weeks of therapy) of Rituxan was used.[30] However, there are instances when cycles were repeated.

Duration of Therapy in GVHD. In most cases, duration of therapy is for one month or less. However, some patients may require repeat authorizations.[30]

Labs/Diagnostics. None required.

6. Immune Thrombocytopenia (ITP).

Criteria. *Patient must meet the following criteria (A AND B)*:[3]

- **A)** Rituxan is prescribed by or in consultation with a hematologist; AND
- **B)** The patient has tried one other therapy (e.g., intravenous immunoglobulin [IVIG], anti-D [RHO] immunoglobulin, corticosteroids, splenectomy).

Guidelines from the American Society of Hematology (ASH) for ITP (2011) mention Rituxan as an appropriate agent for children and adolescents with ITP who have significant on-going bleeding despite treatment with IVIg, anti-D, or corticosteroids.[3] Rituxan is also appropriate as an alternative to splenectomy in children/adolescents with chronic ITP or in patient who do not respond to splenectomy. In adults, Rituxan in recommended for patients with ITP who are at risk for bleeding and who have failed one other line of therapy (e.g., corticosteroids, IVIg, splenectomy).

Dosing in ITP. *Dosing must meet the following:* 375 mg/m^2 IV once weekly.[3,17]

The dose of Rituxan mentioned in the ASH guidelines for ITP is 375 mg/m^2 IV once weekly for four doses.[3] This dose was also evaluated in a Phase III study that treated patients with ITP with Rituxan and dexamethasone.[17] NOTE: Low-dose treatment with Rituxan 100 mg weekly for 4 weeks has been used in a limited number of patients with ITP but clinical efficacy and patient population for this dosing has not been established in a randomized clinical trial.[18] In adults with ITP, studies have found similar efficacy with standard dosing of Rituxan (375 mg/m^2 once weekly for 4 weeks) vs. 1,000 mg on Days 1 and 15 (i.e., the RA regimen).[26-27] These dosing regimens may be considered on a case-by-case basis.

Initial Approval/Extended Approval.

- **A)** *Initial Approval*. Initial approval is for 4 weeks of therapy.[3]
- **B)** *Extended Approval*. Approve for an additional 4 weeks of therapy if 6 months or greater have elapsed since the first dose of the previous Rituxan regimen; the patient responded to therapy (e.g., platelet count increased from baseline following treatment with Rituxan), as determined by the prescribing physician; and the prescribing physician has determined that the patient has relapsed.

Duration of Therapy in ITP. Patients are generally treated with one course of therapy. Retreatment, if necessary, is based on clinical need and the opinion of the prescribing physician.

Labs/Diagnostics. None required.

7. Multiple Sclerosis.

Criteria. *Patient must meet the following criterion (A AND B)*:

A) The patient has tried at least ONE other disease-modifying agent for MS (e.g., Ocrevus™ [ocrelizumab IV infusion], Avonex [interferon beta-1a for intramuscular {IM} injection], Rebif [interferon beta-1a SC injection], Betaseron [interferon beta-1b SC injection], Extavia [interferon beta-1b SC injection], Copaxone [glatiramer acetate SC injection], Glatopa [glatiramer acetate SC injection], Plegridy [peginterferon beta-1a SC injection], Gilenya [fingolimod capsules], Aubagio [teriflunomide tablets], Tecfidera [dimethyl fumarate delayed-release capsules], Lemtrada [alemtuzumab IV injection], or Zinbryta [daclizumab SC injection]); AND

B) Rituxan IV is prescribed by or in consultation with a physician who specializes in the treatment of MS and/or a neurologist.

Rituxan IV has been used for treatment of relapsing and progressive forms of MS. A retrospective observational Swedish study reported on use of Rituxan IV for MS in 557 patients with relapsing-remitting MS, 198 patients with secondary-progressive MS, and 67 patients with **primary progressive MS.**[38] **The majority of patients switched to Rituxan IV following use of other disease-modifying treatment(s).** However, a 96-week, randomized, double-blind, placebo-controlled Phase II/III study (n = 439) failed to show an improvement in time to confirmed disease progression (primary endpoint) in patients with primary progressive MS treated with Rituxan compared with patients who received placebo.[39-42] There are other small studies that suggest Rituxan may have some efficacy in patients with relapsing-remitting MS.

Dosing in MS. *Dosing must meet the following (A OR B):*

A) Initial dose of 500 mg to 2,000 mg (may be divided into two infusions within 1 month).

B) Repeat doses of 500 mg to 2,000 mg IV (may be divided into two infusions within 1 month) if at least 6 months has elapsed since the previous dose.

Initial Approval/Extended Approval.
Initial Approval/Extended Approval. Approve for 1 year.

Duration of Therapy in MS. Indefinite.

Labs/Diagnostics. None required.

8. Neuromyelitis Optica (NMO).

Criteria. *Patient must meet the following criterion (A)*:

A) Rituxan is prescribed by or in consultation with a neurologist.

NMO is an autoimmune inflammatory disease on the central nervous system which is characterized by severe attacks of optic neuritis and longitudinally extensive transverse myelitis.[32] Guidelines for the treatment of transverse myelitis note that Rituxan should be considered to decrease the number of relapses in patients with transverse myelitis due to NMO.[33]

Dosing in NMO. *Dosing must meet the following:*[32]

- **A)** *Induction*.
  - **i.** 375 mg/m^2 IV once weekly; OR
  - **ii.** 1,000 mg infused twice within 2 weeks.
- **B)** *Maintenance*.
  - **i.** 375 mg/m^2 as a single dose; OR
  - **ii.** 1,000 mg infused twice within 2 weeks.

Common practice is to administer a single course of Rituxan (375 mg/m^2) for 4 weeks or 1,000 mg infused twice within 2 weeks for induction. Protocols for maintenance therapy differ and may be selected based on the circulating B-cell repopulation.[37] Note: In small numbers of patients, other dosing schedules have been evaluated in the literature and will be evaluated on a case-by-case basis for clinical appropriateness.

Initial Approval/Extended Approval.[32-33]

- ~~**A)**~~ *Initial Approval/Extended Approval.* 1 year.

In one small Phase III study (n = 8), use of Rituxan was shown to decrease the attack rate of NMO from 2.6 to 0 attacks/patient/year. In another study, the median relapse rate decreased from 1.7 to 0 after treatment with Rituxan (median follow-up was 19 months). There is a published retrospective review of 100 patients with relapsing NMO who were treated with Rituxan for ≥ 6 months.[34] Patients were given induction therapy followed by a single Rituxan infusion (375 mg/m^2) whenever the patient was determined to have insufficient memory B cell depletion; therefore, maintenance dose of Rituxan was administered whenever the frequency of reemerging CD27 memory B cells in peripheral blood mononuclear cells (measured with flow cytometry) exceeded 0.05% in the first 2 years and 0.1% thereafter. The median number of retreatments after induction (median period was 67 months [range, 9 to 108 months]) was 7 treatments (range, 1 to 17 treatments) and mean interval between treatments was 29 weeks.

Duration of Therapy in NMO. Indefinite if the patient is responding to therapy. In the literature, there is documentation of patients using Rituxan for NMO for up to 7 years.[34]

Labs/Diagnostics. None required.

9. Systemic Lupus Erythematous (SLE) [Lupus].

Criteria. *Patient must meet the following criteria (A AND B)*:[1,4-5,19]

- **A)** Rituxan is prescribed by or in consultation with a rheumatologist, nephrologist, or neurologist; AND
- **B)** The patient meets ONE of the following conditions (i or ii)
  - **i.** The patient has neuropsychiatric manifestations of SLE AND has tried at least ONE other therapy (e.g., at least one antidepressant, antipsychotic, corticosteroid, immunosuppressant, or plasma exchange); OR

ii. The patient has lupus nephritis AND has tried at least ONE immunosuppressant (e.g., mycophenolate mofetil, cyclophosphamide, azathioprine,).

EULAR has recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations (2010) which mention Rituxan as a therapeutic option for patients with neuropsychiatric SLE refractory to standard immunosuppressive therapies.[4] Rituxan is used in patients with a refractory acute confusional state or other psychiatric disorders (e.g., lupus psychosis), and in severe peripheral nervous system disorders (e.g., polyneuropathy, mononeuropathy, acute inflammatory demyelinating polyradiculoneuropathy, myasthenia gravis, plexopathy). EULAR in combination with the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) has recommendations for the management of adult and pediatric lupus nephritis (2012).[19] Mycophenolate mofetil or low-dose IV cyclophosphamide are recommended as initial treatment in patients with Class III_A or $III_{A/C}$ and Class IV_A or $IV_{A/C}$ lupus nephritis. For patients who do not respond to these agents, Rituxan is listed as an alternative. Other immunosuppressants listed as therapeutic options for patients with lupus nephritis include cyclosporine, azathioprine, hydroxychloroquine, and tacrolimus. The ACR also has recommendations for management of lupus nephritis (2012).[5] ACR notes that Rituxan may be appropriate in certain patients with lupus nephritis who have tried mycophenolate mofetil and cyclophosphamide and in patients whose nephritis fails to improve or worsens following 6 months of one induction therapy.

Dosing in SLE. *Approve the requested dose.*

There are limited data evaluating Rituxan in patients with various forms of SLE. In one Phase III study that included patients with active proliferative lupus nephritis, the dose used was 1,000 mg administered as an IV infusion on Days 1, 15, 168, and 182.[20] In a limited number of pediatric patients, alternative dosages based on body surface area (BSA) [dosed in mg/m^2] have been evaluated (e.g., 187.5 mg/m^2 for one dose followed by 375 mg/m^2 for three weekly doses) and should also be considered for approval.[21]

Initial Approval/Extended Approval.

A) *Initial Approval.* Initial approval is for 1 month, which is an adequate duration to receive one course of Rituxan.

B) *Extended Approval*: Approve an additional 1 month (which is an adequate duration to receive an additional course of Rituxan) if 6 months or greater have elapsed since the first dose of the previous Rituxan regimen, and the patient has responded to therapy, as determined by the prescribing physician.

Duration of Therapy in SLE. Indefinite if the patient is responding to therapy.

Labs/Diagnostics. None required.

10. Patient has been Established on Rituxan. Approve if the patient meets the conditions for coverage required for **Dosing**, **Extended Approval**, **Duration of Therapy**, and **Labs/Diagnostics** for an approved use in this *Rituxan Utilization Review* policy.

11. **Other Cancer-Related Indications.** Forward to the Medical Director for review on a case-by-case basis. Examples of other indications supported in the *NCCN Compendium*, mainly with category 2A or 2B recommendations, include: acute lymphoblastic leukemia (ALL), central nervous system (CNS) cancers (leptomeningeal metastases, primary CNS lymphoma), Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma, and Hodgkin's lymphoma (e.g., nodular lymph predominant Hodgkin's disease).[6]

Waste Management for All Indications.
Dosing is either a standard dose (e.g., 1,000 mg/dose) or the dose is based on body surface area (kg/m^2).

- If a standard dose is used, use the lowest amount of Rituxan possible to achieve the dose required.
- If the dose is based on body surface area, the dose should be calculated and the number of vials needed assessed.

Conditions Not Recommended for Approval.
Rituxan has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Concurrent Use with A Biologic Disease-Modifying Antirheumatic Drug (DMARD) or Targeted Synthetic DMARD.** Rituxan should not be administered in combination with another biologic agent for an inflammatory condition (e.g., Actemra® [tocilizumab for IV infusion], Kineret® [anakinra for SC injection], Orencia® [abatacept for IV infusion, abatacept for SC injection], or a TNF antagonist [e.g., Cimzia, Enbrel, Humira, Remicade, Simponi, or Simponi Aria]). Combination therapy with two biologic agents is not recommended due to a higher rate of adverse effects with combinations and lack of additive efficacy.[9,22] Xeljanz should not be used in combination with biologic DMARDs such as Rituxan.[23] Targeted synthetic DMARDs (e.g., Xeljanz, Otezla) do not have data supporting use in combination with biologic DMARDs. Due to similar safety concerns (i.e., increased risk of AEs) plus lack of evidence of additive efficacy, targeted synthetic DMARDs should not be used in combination with biologic DMARDs such as Rituxan. Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Rituxan.
2. **Current Use with Disease-Modifying Agents Used for Multiple Sclerosis (MS).** Rituxan has not been evaluated in combination with other disease-modifying agents used for MS (e.g., Ocrevus, Avonex, Betaseron, Extavia, Rebif, Plegridy, Copaxone, Glatopa, Gilenya, Aubagio, Tecfidera, Tysabri, Lemtrada, or Zinbryta); therefore, safety and efficacy have not been adequately established. The concomitant use of Rituxan IV with other immune-modulating or immunosuppressive therapies is anticipated to increase the risk of immunosuppression.

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WAC	WAC 284-43-2050
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Contract Citation	☒ WAH ☒ IMC ☒ MA
Other Requirements	
NCQA Elements	

Revision History

Revision Date	Revision Description	Revision Made By
01/13/2016	New	Kelly Force; Yusuf Rashid, RPh
01/20/2016	Approval	MMLT
01/12/2017	No revisions	Fran McGaugh
01/13/2017	Approval	MMLT
07/24/2017	Criteria completely updated and revised	Michael Sporck, Pharmacy Intern Sophia Yun, PharmD

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03/09/2018	Reassigned from UM140 to PM129	Cindy Bush
04/27/2018	Transferred to new template	Cindy Bush
05/22/2018	Revised	Jennifer Farley, PharmD
06/14/2018	Approval	UM Committee