Rituximab

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Link to Codes

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Clinical Indications

- Rituximab may be indicated when **ALL** of the following are present(1):
  - Clinical diagnosis of **1 or more** of the following:
    - Acute lymphoblastic leukemia and **ALL** of the following(75)(76)(77):
      - Administered in combination with other chemotherapeutic agents
      - B-cell precursor disease
      - CD20-positive and Philadelphia chromosome-negative disease
      - Previously untreated disease
    - ANCA-associated vasculitis (ie, granulomatosis with polyangiitis or microscopic polyangiitis) and **ALL** of the following(78)(79)(80)(81)(82):
      - Age 2 years or older
      - Treatment scenario, as indicated by **1 or more** of the following:
        - Active severe, relapsed, or refractory disease present (eg, progressive glomerulonephritis, alveolar hemorrhage, vasculitic neuropathy), and administered in combination with glucocorticoids, with or without avacopan(89)(94)(95)

- Maintenance therapy, and administered as monotherapy
- Autoimmune hemolytic anemia refractory to corticosteroids(96)(97)(98)N
- Chronic lymphocytic leukemia, CD20-positive, and **ALL** of the following[A](103)(104)(105)(106):N
  - Age 18 years or older
  - Administered in combination with other agents (eg, fludarabine, cyclophosphamide, bendamustine, idelalisib, venetoclax, ibrutinib)(112)
  - Administration needed for **1 or more** of the following:
    - Previously untreated symptomatic disease
    - Relapsed or refractory disease
- Hodgkin lymphoma (nodular lymphocyte-predominant), as indicated by **1 or more** of the following(113)(114)(115):N
  - Maintenance therapy when administered as single agent (for 2 years)
  - Previously untreated disease
  - Refractory disease or suspected relapse
- Immune thrombocytopenia, as indicated by **ALL** of the following(117)(118)(119)(120):N
  - Disease activity and treatment scenario includes **1 or more** of the following:
    - For adults: platelet count less than 30,000/mm^3 (30 $x10^9$/L)(124)(125)
    - For children or adults: significant or persistent bleeding associated with low platelet count (eg, less than 50,000/mm^3 (50 $x10^9$/L))
  - Failure of or contraindication to therapy with **1 or more** of the following(125)(126):
    - Anti-D immunoglobulin
    - Corticosteroids
    - IVIG
    - Splenectomy
- Non-Hodgkin lymphoma, as indicated by **1 or more** of the following(127)(128)(129)(130):N
  - Initial course of rituximab and **ALL** of the following[B]:
    - CD20-positive B-cell non-Hodgkin lymphoma
    - Clinical scenario, as indicated by **1 or more** of the following:
      - Burkitt lymphoma, Burkitt-like lymphoma, or mature B-cell acute leukemia, as indicated by **ALL** of the following(77)(128)(146)(147):
        - Age 6 months or older
        - Previously untreated disease and administered in combination with first-line chemotherapy(148)
      - Diffuse large B-cell lymphoma, as indicated by **ALL** of the following(128)(149)(150)(151):
        - Age 6 months or older
        - Previously untreated disease and administered in combination with first-line chemotherapy
      - Follicular lymphoma, as indicated by **ALL** of the following(128)(152)(153)(154)(155)(156):
        - Age 18 years or older
        - Administered in combination with first-line chemotherapy
      - Mantle cell lymphoma, as indicated by **ALL** of the following(157):
        - Adult patient age 65 years or younger(136)
        - Clinical scenario, as indicated by **1 or more** of the following:
          - Previously untreated disease and administered in combination with first-line chemotherapy(158)
          - Relapsed disease or refractory to at least one prior therapy(159)
      - Marginal zone lymphoma (gastric and nongastric mucosa-associated lymphoid tissue (MALT), nodal marginal zone lymphoma, splenic marginal zone lymphoma), as indicated by **ALL** of the following(128)(160)(161):

- Age 18 years or older
- Systemic treatment scenario, as indicated by **1 or more** of the following:
  - Administered in combination with bendamustine
  - Administered in combination with CHOP chemotherapy regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone)
  - Administered in combination with CVP chemotherapy regimen (cyclophosphamide, vincristine, and prednisone)
  - Administered as monotherapy or in combination with chlorambucil or cyclophosphamide for patient who cannot tolerate first-line therapy (eg, elderly or infirm patient)

- Nonprogressing low-grade disease, as indicated by **ALL** of the following(1):
  - Age 18 years or older
  - Clinical scenario, as indicated by **1 or more** of the following:
    - Complete response after first-line treatment with 6 to 8 cycles of cyclophosphamide, vincristine, and prednisone
    - Partial response[C] after first-line treatment with 6 to 8 cycles of cyclophosphamide, vincristine, and prednisone
    - Stable disease after first-line treatment with 6 to 8 cycles of cyclophosphamide, vincristine, and prednisone

- Subsequent course of rituximab and **ALL** of the following[B](1):
  - CD20-positive B-cell non-Hodgkin lymphoma
  - Clinical scenario, as indicated by **1 or more** of the following:
    - Burkitt lymphoma, Burkitt-like lymphoma, or mature B-cell acute leukemia, with favorable response to prior first-line therapy with rituximab and chemotherapy
    - Diffuse large B-cell lymphoma, with favorable response to prior first-line therapy with rituximab and chemotherapy[D](149)(162)
    - Follicular lymphoma, with favorable response to prior first-line therapy with rituximab, and **1 or more** of the following(156):
      - Maintenance treatment(128)(153)(163)
      - Relapsed or refractory disease(164)(165)(166)
    - Mantle cell lymphoma, with favorable response to prior treatment with rituximab(158)
    - Marginal zone lymphoma (gastric and nongastric mucosa-associated lymphoid tissue (MALT), nodal marginal zone lymphoma, splenic marginal zone lymphoma) requiring systemic therapy, with favorable response to prior treatment with rituximab, as indicated by **1 or more** of the following(161):
      - Administered as monotherapy for patient who cannot tolerate first-line therapy (eg, elderly or infirm patient)
      - Administered as combination therapy

- Pemphigus and **ALL** of the following(167)(168)(169)(170)(171):N
  - Age 18 years or older
  - Clinical scenario, as indicated by **1 or more** of the following:
    - Initial therapy, and administered with corticosteroids
    - Maintenance therapy

- Post-transplant lymphoproliferative disorder after solid organ transplant and **ALL** of the following(174):N
  - CD20-positive B-cell disease
  - Disease activity and treatment scenario includes **1 or more** of the following:
    - Adult with failure to respond to reduction of immunosuppressive therapy(128)
    - Child with **1 or more** of the following(175)(178)(179):

- Failure to respond to reduction of immunosuppressive therapy
- High risk of rejection with reduction of immunosuppressive therapy
- Persistent or progressive post-transplant lymphoproliferative disorder in absence of allograft rejection

− Rheumatoid arthritis, as indicated by **1 or more** of the following(180)(181)(182)(183)(184)(185):N

- Initial course of rituximab and **ALL** of the following:
  - Age 18 years or older
  - Administered in combination with methotrexate, unless unable to tolerate methotrexate
  - Moderate to severe active rheumatoid arthritis,[E] as indicated by **1 or more** of the following(194)(195):
    - Clinical Disease Activity Index[F] score greater than 10
    - Disease Activity Score using 28-joint counts (DAS28)[G] of 3.2 or greater
    - Patient Activity Scale-II[H] of 3.71 or greater
    - Routine Assessment of Patient Index Data 3[I] score of 7 or greater
    - Simplified Disease Activity Index[J] score greater than 11
- Subsequent course of rituximab and **ALL** of the following:
  - Age 18 years or older
  - Administered in combination with methotrexate, unless unable to tolerate methotrexate
  - Favorable response to prior administration of rituximab

− Thrombotic thrombocytopenic purpura and **ALL** of the following(196)(197):N

- Age 18 years or older
- Disease severity includes **1 or more** of the following:
  - Acute disease with either cardiac (eg, increased troponin) or neurologic pathology
  - Recurrent disease
  - Refractory disease (ie, to plasma exchange and corticosteroids)

− Waldenstrom macroglobulinemia, as indicated by **1 or more** of the following(198)(199)(200)(201):N

- Initial course of rituximab and **ALL** of the following(198)(204)(205)(206):
  - Age 18 years or older
  - Administered as single agent or in combination with other agents
  - Primary therapy needed(207)
- Subsequent course of rituximab and **ALL** of the following(198):
  - Age 18 years or older
  - Partial or complete response[K] to initial course of rituximab, as evidenced by **ALL** of the following(208):
    - Fifty percent or greater reduction in adenopathy and/or organomegaly, if present with initial treatment, on physical examination or CT scan
    - Fifty percent or greater reduction of serum monoclonal IgM protein by serum electrophoresis
    - No new symptoms or signs of disease
  - Response to initial rituximab course lasted at least 12 months.(209)

- No active hepatitis B virus (HBV) infection (ie, hepatitis B surface antigen and hepatitis B core IgM negative)(198)
- No concurrent use of live vaccine
- No severe or active infection (eg, cellulitis, colitis, pneumonia, sepsis, urinary tract infection)(210)(211)
- No untreated latent or active tuberculosis(180)(210)

Evidence Summary

Background

Rituximab is a recombinant monoclonal antibody that results in cell death of B-lymphocytes by targeting the CD20 protein expressed on the lymphocyte surface.(1) **(EG 2)** Potential adverse events that may occur secondary to treatment with rituximab include JC virus infection resulting in progressive multifocal leukoencephalopathy, hepatitis B virus reactivation, infusion reaction, tumor lysis syndrome (in patients with non-Hodgkin lymphoma), and severe mucocutaneous reaction.(1)(2) **(EG 2)**

Criteria

The evidence for the clinical indications found in this guideline includes 166 published peer reviewed articles, 21 specialty society or other evidence-based guidelines, and 11 Cochrane systematic reviews.

For acute lymphoblastic leukemia, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A multicenter randomized trial of 209 adults (18 to 59 years of age) with CD20-positive, Philadelphia chromosome-negative, B-cell precursor, acute lymphoblastic leukemia who received chemotherapy with or without rituximab found that 2-year event-free survival was significantly longer in the rituximab group (65%) as compared with the control group (52%), with similar incidence of severe adverse events.(75) **(EG 1)** Expert consensus guidelines recommend rituximab in combination with other agents for treatment of CD20-positive, B-cell lineage, acute lymphoblastic leukemia in patients 15 to 59 years of age; patients 60 years of age and older had a high incidence of death.(76) **(EG 2)**

For ANCA-associated vasculitis, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** Randomized controlled studies found that rituximab was noninferior to, but not superior to, cyclophosphamide in achieving complete remission after 6, 12, and 18 months.(83)(84)(85) **(EG 1)** A randomized controlled trial assigned 115 such patients to either rituximab or azathioprine; relapse rates after 28 months were significantly better with rituximab (5% vs 29%, respectively), with comparable adverse event rates in each group.(86) **(EG 1)** A randomized trial of 97 patients with ANCA-associated vasculitis (all of whom had achieved complete remission after an 18-month maintenance regimen) compared continued maintenance with biannual rituximab or placebo and found, at 28-month follow-up, that rituximab was associated with higher relapse-free survival rates compared with placebo.(87) **(EG 1)** An open-label randomized trial of 170 patients with relapsed ANCA-associated vasculitis who achieved remission within 4 months of rituximab plus corticosteroid reinduction therapy compared maintenance treatment with either rituximab or azathioprine and found, at 36 months of follow-up, that rituximab was associated with lower rates of disease relapse compared with azathioprine.(88) **(EG 1)** Specialty society guidelines and technology assessments endorse the use of rituximab for induction and maintenance of remission.(79)(89)(90)(91)(92) **(EG 2)** Effectiveness of rituximab has been demonstrated for up to 5 years in randomized controlled trials.(90) **(EG 2)** In the setting of recurrent ANCA-associated vasculitis leading to glomerulonephritis after kidney transplant, case series indicate that rituximab administration is associated with biopsy-proven remission induction as well.(93) **(EG 2)**

For autoimmune hemolytic anemia refractory to corticosteroids, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A meta-analysis of 21 studies suggested possible short-term efficacy for the use of rituximab in autoimmune hemolytic anemia refractory to steroids. Findings were limited by significant heterogeneity, small patient numbers, and a lack of randomized controlled trials.(99) **(EG 1)** A phase III randomized trial of 32 patients with newly diagnosed warm autoimmune hemolytic anemia compared corticosteroids combined with rituximab or placebo and found that rituximab was associated with higher 1-year overall response rates and 2-year complete response rates compared with placebo.(97) **(EG 1)** A randomized controlled trial of 64 patients with newly diagnosed warm-antibody autoimmune hemolytic anemia assigned patients to treatment with either prednisolone alone or prednisolone plus rituximab. After 12 months, a satisfactory response was observed in 36% of those on prednisolone alone but in 75% of those on prednisolone plus rituximab; after 36 months, 70% of patients receiving rituximab were in remission, as compared with 45% on prednisolone alone.(98) **(EG 1)** Review articles and a subspecialty practice guideline note that rituximab is the preferred second-line choice for the treatment of corticosteroid-refractory autoimmune hemolytic anemia.(96)(100)(101)(102) **(EG 2)**

For chronic lymphocytic leukemia that is CD20-positive, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** A phase III trial (525 patients age 65 years or older with treatment-naive chronic lymphocytic leukemia) compared maintenance rituximab with observation after induction with the combination of fludarabine, cyclophosphamide, and rituximab and found, at a median follow-up of 47.7 months, that maintenance rituximab was associated with improved progression-free survival.(107) **(EG 1)** An open-label phase III randomized trial of 771 patients with previously untreated chronic lymphocytic leukemia compared treatment with rituximab combined with either ibrutinib or fludarabine plus cyclophosphamide and found, at a median follow-up of 53 months, that ibrutinib was associated with improved progression-free survival compared with fludarabine plus cyclophosphamide, with no difference in overall survival seen between the 2 groups.(108) **(EG 1)** A phase III randomized trial of 529 previously untreated patients with chronic lymphocytic leukemia compared the combination of rituximab plus ibrutinib with chemoimmunotherapy (combination rituximab, fludarabine, and cyclophosphamide) and found, at a median follow-up of 33.6 months, that ibrutinib was associated with longer progression-free and overall survival compared with chemoimmunotherapy.(109) **(EG 1)** Review articles and systematic reviews of randomized controlled trials reported efficacy of rituximab in significantly improving progression-free and overall survival in both previously treated and untreated patients when added to chemotherapy with fludarabine and cyclophosphamide.(105)(110)(111) **(EG 1)** An expert consensus guideline recommends rituximab in combination with other agents for previously untreated and relapsed disease.(103) **(EG 2)**

For Hodgkin lymphoma (nodular lymphocyte-predominant), evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A retrospective review of 59 patients with nodular lymphocyte-predominant Hodgkin lymphoma found that treatment with the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) resulted in an overall response rate of 100% and estimated 5-year and 10-year progression-free survival rates of 88.5% and 59.3%, respectively. Larger prospective studies were recommended.(116) **(EG 2)** A literature review indicates that rituximab may be used alone for patients with stage I nodular lymphocyte-predominant Hodgkin lymphoma, and may be used for patients with advanced stage disease as part of combination chemotherapy.(113) **(EG 2)** An expert consensus guideline recommends rituximab in addition to chemotherapy and involved-site radiation therapy for patients with nodular lymphocyte-predominant Hodgkin lymphoma; for patients treated with rituximab as a single agent, it can be used as maintenance therapy for 2 years.(114) **(EG 2)**

For immune thrombocytopenia, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A systematic review and meta-analysis of 5 high-quality trials found strong evidence that rituximab can significantly improve platelet count in patients with immune thrombocytopenia, although evidence for a sustained response beyond 6 to 12 months is limited.(121) **(EG 1)** Expert consensus guidelines recommend rituximab as a treatment option for selected children and adults who fail first-line medical therapy in lieu of splenectomy or for whom splenectomy has failed.(122)(123) **(EG 2)**

For non-Hodgkin lymphoma, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** Expert reviews and meta-analyses of randomized controlled trials found rituximab to be effective in improving the response rate, as well as progression-free and overall survival, in adults with CD20-positive B-cell non-Hodgkin lymphoma,(128) with much more limited information available for children.(127)(130)(131) **(EG 1)** A phase III trial randomized 240 patients with mantle cell lymphoma to rituximab maintenance or observation after immunochemotherapy and autologous stem cell transplant and found, at a median follow-up of 50 months, that maintenance rituximab was associated with prolonged event-free, progression-free, and overall survival compared with observation.(132) **(EG 1)** An extension of this study found, at a median follow-up of 7 years, that rituximab maintenance therapy was associated with continued prolonged event-free and progression-free survival and similar overall survival rates compared with observation.(133) **(EG 1)** A multicenter prospective trial of 63 patients with previously untreated mantle cell lymphoma found that rituximab, in combination with other chemotherapeutic agents, was associated with an estimated 5-year survival rate of 73% and progression-free survival rate of 61%.(134) **(EG 2)** A multicenter phase II trial of 38 untreated mantle cell lymphoma patients found, after a median follow-up of 30 months, that administration of rituximab with lenalidomide yielded an overall response rate of 92%, a complete response rate of 64%, and estimated 2-year progression-free and overall survival rates of 85% and 97%, respectively; responses to therapy were also significantly associated with improved quality of life.(135) **(EG 1)** A multicenter phase II trial of 49 patients with advanced stage, previously untreated mantle cell lymphoma found that rituximab, when given in combination with other chemotherapeutic agents, was associated with a median progression-free survival of 4.8 years and a median overall survival of 6.8 years.(136) **(EG 2)** A phase III randomized controlled trial of 260 adults with untreated Burkitt lymphoma or leukemia found that those assigned to chemotherapy with rituximab had a significantly increased 3-year event-free survival rate as compared with those assigned to chemotherapy without rituximab (75% vs 62%, respectively).(137) **(EG 1)** A systematic review and meta-analysis found no evidence of an increase in second primary malignancy after initial treatment of non-Hodgkin lymphoma with rituximab.(138) **(EG 1)** Longer-term follow-up of patients with follicular lymphoma who achieved at least an initial partial response found that

maintenance rituximab for up to 5 years did not significantly improve event-free or overall survival, and did exhibit increased toxicity, especially infections.(139) **(EG 1)** However, a subsequent meta-analysis of individual patient data from prior randomized studies estimates that overall survival may be improved by maintenance therapy with rituximab in patients with follicular lymphoma.(140) **(EG 1)** Long-term follow-up of 609 patients with follicular lymphoma, all of whom had responded to induction chemotherapy and were then randomized to either 2 years of maintenance rituximab or observation, found, at 9-year follow-up, that rituximab was associated with longer progression-free survival compared with observation, with no difference in overall survival seen between the groups.(141) **(EG 1)** Retrospective studies of patients with primary nodal marginal zone lymphoma and extragastric mucosa-associated lymphoid tissue (MALT) found that treatment with rituximab plus bendamustine resulted in a complete response rate of 71%.(142)(143) **(EG 2)** A review article noted that rituximab in combination with other agents is an important treatment for patients with newly diagnosed or relapsing MALT lymphoma.(144) **(EG 2)** A single-arm phase II study of 53 patients with aggressive diffuse large B-cell lymphoma (all with MYC gene rearrangement, 24 with a concomitant rearrangement of BCL2, BCL6, or both (ie, double-hit)) evaluating the efficacy of treatment with the combination of etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (EPOCH-R) found, at a median follow-up of 55.6 months, 48-month event-free and overall survival rates of 71% and 76.7%, respectively.(145) **(EG 2)** An open-label phase III randomized trial of 328 pediatric patients with high-risk mature B-cell non-Hodgkin lymphoma (most patients had Burkitt lymphoma) compared a standard Lymphome Malin B (LMB) chemotherapy protocol with and without rituximab and found, at 39.9-month follow-up, that rituximab was associated with longer event-free survival compared with LMB, and that 3-year overall survival rates were higher in the rituximab group (95.1% and 87.3% in the rituximab and LMB groups, respectively). (146) **(EG 1)**

For pemphigus, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A network meta-analysis of 10 studies (592 patients) evaluating steroid-sparing adjuvant treatment of pemphigus found that rituximab was the most effective therapy for inducing disease remission, reducing relapse rates, and reducing total corticosteroid usage. The authors noted that the lack of double-blind studies and heterogeneity among the included studies limited the results, and further trials were recommended.(172) **(EG 1)** A randomized trial of 135 patients with moderate to severe active pemphigus vulgaris treated patients with a tapering schedule of glucocorticoids and either rituximab or mycophenolate mofetil and found, at 52-week follow-up, that rituximab was associated with more patients achieving sustained complete remission (as measured by a score of 0 on the Pemphigus Disease Area Index for at least 16 weeks after cessation of glucocorticoids) and lower cumulative glucocorticoid dose compared with mycophenolate mofetil.(173) **(EG 1)** A multicenter open-label randomized trial of 90 adults with newly diagnosed pemphigus compared treatment with either prednisone monotherapy (tapered over 12 to 18 months) or prednisone (tapered over 3 to 6 months) combined with rituximab and found, at 24-month follow-up, that rituximab was associated with a higher rate of complete remission compared with prednisone alone (89% vs 34% in the rituximab and prednisone monotherapy groups, respectively). In addition, rituximab was associated with a lower rate of serious adverse events compared with prednisone monotherapy.(167) **(EG 1)**

For post-transplant lymphoproliferative disorder after solid organ transplant, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** An open-label multicenter phase II study of 70 patients with CD20-positive disease unresponsive to immunosuppression reduction reported a median overall survival of 6.6 years in patients treated with rituximab followed by anthracycline-based chemotherapy.(174) **(EG 2)** Oncology practice guidelines and review articles recommend that rituximab is a therapeutic option in patients with post-transplant lymphoproliferative disorder that fails to respond to reduction in immunosuppressive therapy.(128)(175)(176)(177) **(EG 2)**

For rheumatoid arthritis, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** Expert reviews and meta-analyses of randomized controlled trials found rituximab to be effective in slowing progression as well as in reducing signs and symptoms in patients with moderate to severe active disease, with a favorable risk-benefit relationship in those who have failed therapy with at least one tumor necrosis factor inhibitor.(180)(181)(183)(186) **(EG 2)** Long-term follow-up of patients treated with rituximab has been favorable, with continuing effectiveness demonstrated after as long as 9.5 years of therapy for patients with an inadequate response to methotrexate for whom conventional disease-modifying antirheumatic drugs have failed.(180) **(EG 2)** An open-label, randomized controlled noninferiority trial of 329 patients with active rheumatoid arthritis not previously treated with methotrexate, sulfasalazine, or leflunomide compared treatment with rituximab and tumor necrosis factor inhibitors; the protocol allowed clinicians to change treatment strategies after randomization. At 1-year follow-up, both groups had comparable achievement of disease remission, as measured by the Disease Activity Score using 28-joint counts (DAS28-ESR) and American College of Rheumatology (ACR) response criteria.(187) **(EG 1)** A phase III randomized trial of 511 patients with active rheumatoid arthritis (all of whom had an inadequate response to methotrexate and no prior treatment with a biologic drug) compared treatment with methotrexate combined with either rituximab or placebo and found, at 24-week follow-up, that rituximab was associated with more patients achieving a 20% or 50% improvement in ACR scores.(188) **(EG 1)** A

randomized double-blind controlled study of 755 methotrexate-naive patients with active rheumatoid arthritis found, at 52-week follow-up, that treatment with methotrexate plus rituximab was associated with reduced progression of joint damage and increased clinical response, as measured by ACR response criteria, compared with treatment with methotrexate plus placebo.(189) **(EG 1)** Specialty society consensus guidelines indicate that there is sufficient evidence to support the use of rituximab in rheumatoid arthritis patients not previously treated with tumor necrosis factor inhibitors.(181)(190)(191) **(EG 2)** An observational study of 493 patients with active rheumatoid arthritis who had not previously responded to methotrexate and had not achieved remission (as measured by DAS28-ESR) after a 24-week course of rituximab compared retreatment with rituximab at 24-week intervals with retreatment at physician's discretion and found that the treatment protocol resulted in significantly more patients achieving a major clinical response and reduced incidence of rheumatoid arthritis flares.(192) **(EG 2)** A specialty consensus guideline states that repeat treatment with rituximab should be considered for patients who do not reach remission or at least low-level disease activity. (190) **(EG 2)**

For thrombotic thrombocytopenic purpura, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** An expert consensus guideline recommends rituximab in conjunction with plasma exchange and corticosteroids for acute disease with cardiac or neurologic pathology, or for patients with refractory or recurrent immune-mediated disease.(196) **(EG 2)** A multicenter phase II study of 40 patients demonstrated significantly fewer relapses for patients initially treated with plasma exchange and weekly rituximab for 4 weeks (10% relapse, median time to relapse of 27 months) as compared with historical controls treated with plasma exchange with or without steroids (57% relapse, median time to relapse of 18 months).(197) **(EG 2)**

For Waldenstrom macroglobulinemia, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care. **(RG A2)** A systematic review and meta-analysis of 22 studies (806 patients) evaluating the efficacy of rituximab-based chemotherapy for the treatment of Waldenstrom macroglobulinemia found overall response, major response (defined as the sum of complete response, very good partial response (90% or greater decrease in serum IgM), and partial response (50% or greater decrease in IgM)), and complete response rates of 84%, 71%, and 7%, respectively.(202) **(EG 1)** A retrospective database review of 1310 patients (all age 65 years or older) initiating chemotherapy for Waldenstrom macroglobulinemia or lymphoplasmacytic lymphoma found that rituximab, either alone or in combination with other immunochemotherapy, was associated with better overall survival and lower risk of transfusions, with no difference in rates of hospitalization or plasmapheresis, compared with regimens without rituximab. (203) **(EG 2)** Consensus guidelines recommend rituximab as initial therapy for symptomatic patients; rituximab may be used alone or in combination with other chemotherapeutic drugs such as a proteasome inhibitor (eg, bortezomib), or with a kinase inhibitor such as ibrutinib, or with an alkylating agent such as bendamustine or cyclophosphamide.(198)(200) **(EG 2)**

Inconclusive or Non-Supportive Evidence

For CNS lymphoma (primary), evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A meta-analysis of 8 studies (2 randomized trials and 6 retrospective studies with a total of 753 patients) evaluating rituximab-containing regimens for primary CNS lymphoma found that rituximab was associated with improved complete response, 2-year and 5-year overall survival, and progression-free survival rates. However, due to heterogeneity between studies and the paucity of included randomized studies, the authors recommended further large randomized trials.(3) **(EG 1)** A phase III randomized study of 199 patients with newly diagnosed primary CNS lymphoma compared induction combination chemotherapy (methotrexate, carmustine, teniposide, and prednisone) with and without rituximab and found, at a median follow-up of 32.9 months, no difference in event-free survival, progression-free survival, or response rates between the groups.(4) **(EG 1)** A nonrandomized phase II trial treated 52 patients with newly diagnosed primary CNS lymphoma with a combination of rituximab, methotrexate, procarbazine, and vincristine (followed by reduced-dose whole brain radiotherapy and cytarabine in 31 patients who responded) and found a median progression-free survival of 7.7 years and 3.3 years in responders and nonresponders, respectively.(5) **(EG 2)** Expert consensus guidelines recommend rituximab, alone or in combination with other cytotoxic agents, for the initial treatment of primary CNS lymphoma.(6)(7) **(EG 2)**

For cutaneous B-cell lymphoma, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A European consensus guideline noted that while a number of case series suggest a role for rituximab for this condition,

adequate randomized controlled trials have not been reported.(8) **(EG 2)** An expert consensus guideline includes rituximab as a treatment option for generalized cutaneous B-cell lymphoma without extracutaneous disease.(9) **(EG 2)**

For demyelinating polyneuropathy associated with IgM monoclonal gammopathy, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review and meta-analysis identified 2 double-blind randomized placebo-controlled trials with 80 patients and found low-quality evidence to support the use of rituximab for demyelinating polyneuropathy associated with IgM monoclonal gammopathy. The authors concluded that larger randomized controlled trials with valid outcome measures are needed.(10) **(EG 1)**

For dermatomyositis, polymyositis, and inflammatory myopathies, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review and meta-analysis of 17 studies (362 patients) evaluating rituximab for the treatment of idiopathic inflammatory myositis found an overall pooled response rate of 70% (with complete remission in 13%) and high response rates in all myositis subtypes, including polymyositis (69%), dermatomyositis (67%), antisynthetase syndrome (70%), juvenile dermatomyositis (60%), and immune-mediated necrotizing myopathy (86%). However, the authors noted that the results were limited by heterogeneity of response rate measurements and the small number of included patients; further randomized studies with objective measures, larger patient numbers, and longer follow-up were recommended.(11) **(EG 1)**

For graft vs host disease, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review of the use of rituximab found only nonrandomized studies with small numbers of patients and varying criteria for reporting outcomes, and it could not reach definitive conclusions on the overall effectiveness of rituximab for this condition.(12) **(EG 1)** However, a subsequent retrospective review of 435 B-cell lymphoma patients who had received allogeneic peripheral blood stem cell transplant found that the cohort that received rituximab within 6 months of transplant, as compared with the cohort that did not, showed significant improvement in acute graft vs host disease, treatment-related mortality, progression-free survival, and overall survival, with no worsening in chronic graft vs host disease. The authors suggest that additional prospective studies be undertaken.(13) **(EG 2)** A phase II study assigned 65 patients with graft vs host disease after allogeneic stem cell transplant to rituximab at 3, 6, 9, and 12 months after transplant; the rates of chronic graft vs host disease and chronic graft vs host disease requiring corticosteroids at 2 years post transplant were 48% and 31%, respectively, as compared with 60% and 49%, respectively, in a nonrandomized control group that did not receive rituximab. Mortality and survival were both significantly improved after 4 years.(14) **(EG 2)** A subsequent randomized controlled trial of 84 patients receiving allogeneic stem cells randomized half of the patients to receive rituximab in addition to standard prophylaxis for graft vs host disease; after 1 year, there was no significant difference in overall survival or incidence of graft vs host disease between groups.(15) **(EG 1)**

For idiopathic nephrotic syndrome, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review of 8 studies (one open-label randomized trial and 7 case series) with a total of 226 pediatric patients evaluated rituximab for the treatment of steroid-resistant nephrotic syndrome and found an overall primary remission rate of 46.4%, with sustained remission rates varying from 18% to 93.7%. However, the authors noted that, due to the lack of controls and the retrospective nature of most of the included studies, further prospective trials were needed.(16) **(EG 1)** A systematic review evaluating non-corticosteroid immunosuppressive therapy for corticosteroid-sensitive nephrotic syndrome in children included 13 studies of rituximab and found that rituximab reduced the incidence of disease relapse. However, the authors noted that lack of head-to-head studies and long-term data on adverse events limited the results.(17) **(EG 1)** An open-label noninferiority randomized trial including 30 children with corticosteroid-dependent nephrotic syndrome (all of whom were in remission on prednisone) compared continued prednisone with and without a dose of rituximab (followed by corticosteroid taper) and found, at 3-month follow-up, that rituximab was noninferior to corticosteroids for decreasing proteinuria; 1-year relapse-free survival rates were 7% and 87% in the corticosteroid and rituximab groups, respectively. The authors recommended further randomized trials with a superiority design to confirm the results.(18) **(EG 1)** A multicenter randomized trial of 48 patients with either frequently relapsing or steroid-dependent nephrotic syndrome found, after 1 year, that administration of rituximab was associated with a significantly longer relapse-free period than administration of placebo (267 days vs 101 days, respectively), although 42% of patients in the active treatment group had at least one adverse event, as compared with 25% in the placebo group.(19)(20) **(EG 1)** In a study of 10 children and 20 adults with active nephrotic syndrome who were in steroid-induced remission for at least 1 month, patients were administered rituximab in an off-on fashion, with each patient receiving either 1 or 2 doses; after 1 year, all patients were in remission, 18 were entirely off treatment, and 15 never relapsed.(21) **(EG 2)** Review articles indicate that while rituximab appears to have some degree of efficacy for this indication, there are very few randomized controlled studies, and there is significant danger of publication bias; further high-quality randomized trials are needed.(2)(22)(23) **(EG 2)**

For kidney transplant, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review evaluating polyclonal and monoclonal antibodies for the treatment of acute graft rejection identified 2 studies (58 patients) of rituximab and found that, compared with steroids, there was no difference in rates of reversal of initial episode of humoral rejection, graft loss, or patient death; the addition of rituximab to steroids increased the risk of urinary tract infection and pyelonephritis.(24) **(EG 1)** A systematic review of 4 randomized controlled trials and one case series related to the use of rituximab as induction therapy in renal transplant found no convincing evidence of benefit but did find possible safety concerns in terms of leukopenia and cardiovascular mortality; the authors indicated that further trials are required.(25) **(EG 2)** A subsequent systematic review and meta-analysis identified 3 studies involving rituximab for induction therapy in renal transplant and concluded that the drug has an overall uncertain effect on death, graft loss, acute rejection, and other adverse outcomes as compared with placebo.(26) **(EG 1)** A systematic review on the use of rituximab for antibody-mediated rejection found a total of 16 studies, of which 13 were retrospective case reviews. The authors concluded that, although there was limited evidence that rituximab may be useful for acute antibody-mediated rejection, there is insufficient evidence to support its use for chronic antibody-mediated rejection; the authors indicated that additional study is necessary.(27) **(EG 2)**

For membranous nephropathy, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A randomized noninferiority trial of 130 patients with membranous nephropathy compared treatment with either rituximab or cyclosporine and found, at 12-month follow-up, that rituximab was noninferior to cyclosporine for inducing complete or partial remission of proteinuria; at 24-month follow-up, rituximab was associated with more patients maintaining remission compared with cyclosporine. However, the authors noted that the unblinded trial design and the lack of reporting of intention-to-treat outcomes limited the results.(28) **(EG 1)** Case series and review articles indicate that, while off-label use of rituximab for this indication is not uncommon, more rigorous randomized controlled studies are necessary for confirmation of both effectiveness and appropriate dosing.(29)(30)(31) **(EG 2)**

For mixed cryoglobulinemia, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review and meta-analysis evaluating treatments for hepatitis C virus-associated mixed cryoglobulinemia identified 3 randomized trials (118 patients) of rituximab and found that, while treatment likely improved skin vasculitis wounds, there was no difference in kidney disease, peripheral neuropathy, or joint arthralgia. However, the authors noted that only one of the studies evaluated rituximab combined with antiviral therapy and concluded that there was not sufficient evidence to determine the optimal treatment of hepatitis C virus-associated mixed cryoglobulinemia.(32) **(EG 1)** A retrospective case series of 87 patients treated with rituximab reported a complete response in 74% of cases with purpuric skin lesions, 44% of cases with peripheral neuropathy, and 50% of cases with membranoproliferative glomerulopathy. The authors concluded that the role of rituximab for this condition should be confirmed by randomized controlled trials.(33) **(EG 2)** Similar results were seen in a prospective case series of 37 patients.(34) **(EG 2)**

For multiple sclerosis, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review of 28 studies (37,443 patients) evaluating rituximab for the treatment of multiple sclerosis found low-certainty to moderate-certainty evidence that rituximab may reduce relapses in relapsing multiple sclerosis, with insufficient evidence regarding the efficacy of rituximab for treatment of primary progressive disease. The authors noted that the conclusions were limited by the relatively small number of randomized trials and limited evidence on adverse effects, and further studies with longer follow-up were recommended.(35) **(EG 1)** A systematic review and meta-analysis of 15 studies (946 patients) evaluating the efficacy of rituximab for relapsing-remitting multiple sclerosis found that rituximab reduced the annualized relapse rate by 80% and Expanded Disability Status Scale scores by 46%. However, the authors noted that heterogeneity among the included studies limited the results, and large randomized trials were recommended.(36) **(EG 1)** A phase III randomized trial of 200 patients with relapsing-remitting multiple sclerosis (or with a demyelinating episode in conjunction with at least one asymptomatic lesion compatible with multiple sclerosis) compared treatment with either rituximab or dimethyl fumarate and found, at 24-month follow-up, that rituximab was associated with a lower risk of relapse compared with dimethyl fumarate. However, the authors noted that the relatively small and homogeneous study population and the lack of a double-blind study design limited the results, and further trials were recommended.(37) **(EG 1)** Review articles found insufficient evidence to support the use of rituximab for relapsing-remitting multiple sclerosis, and the authors concluded that large-scale studies are needed, especially to optimize therapy dosing regimens.(38)(39)(40)(41) **(EG 1)** For primary progressive multiple sclerosis, a randomized double-blind placebo-controlled trial with 439 patients found that the time to confirmed disease progression did not significantly differ in patients treated with rituximab or placebo, although retrospective subgroup analysis suggests that younger patients, especially those with inflammatory lesions, may benefit. However, this finding must be confirmed with additional prospective trials.(42)(43) **(EG 1)** A retrospective study of 494 patients with newly diagnosed relapsing-remitting multiple sclerosis

evaluating response to initial therapy found that rituximab was associated with lower rates of relapse and drug discontinuation. However, due to the retrospective nature of the study, the authors recommended further prospective trials.(44) **(EG 2)**

For myasthenia gravis, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review found 2 randomized controlled trials (99 patients) evaluating rituximab for the treatment of myasthenia gravis and concluded that there were very uncertain effects on symptom severity and functional ability but moderate-certainty evidence that rituximab reduced relapses requiring rescue therapy over 9 months of follow-up; the authors noted that the results were limited by the short follow-up and small number of included patients and recommended longer prospective studies to confirm the optimal regimens for specific disease subgroups and long-term efficacy and safety.(45) **(EG 1)** An international consensus guideline notes that rituximab should be considered for the treatment of patients with muscle-specific kinase antibody-positive disease refractory to conventional immunotherapy, though its efficacy in acetylcholine receptor antibody-positive disease is uncertain.(46) **(EG 2)**

For neuromyelitis optica spectrum disorder, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A meta-analysis of 26 studies (19 of which were retrospective) with a total of 577 patients evaluating the efficacy of rituximab for treatment of neuromyelitis optica spectrum disorder found that rituximab improved the annualized relapse rate and Expanded Disability Status Scale scores, with 62.9% of patients achieving a relapse-free state. However, the authors noted that the lack of large multicenter studies and heterogeneity among studies regarding coadministered immunotherapies limited the results, and further studies were recommended.(47) **(EG 1)** A randomized trial of 38 patients with corticosteroid-dependent neuromyelitis optica spectrum disorders (all of whom were seropositive for aquaporin 4 (AQP4) antibody) compared treatment with either rituximab or placebo and found, at 72-week follow-up, that rituximab was associated with fewer relapses compared with placebo. However, the authors noted that the small sample size, the inclusion of patients with mild disease, and the inclusion of only patients with AQP4 antibody limited the results.(48) **(EG 1)**

For Sjogren syndrome, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review of 4 randomized controlled trials and 7 nonrandomized trials found that rituximab was not effective in reducing symptoms of fatigue in patients with Sjogren syndrome compared with placebo; the authors noted that the study was limited by the small number of randomized trials and the heterogeneity of outcome measures used to assess fatigue.(49) **(EG 1)** A systematic review and meta-analysis identified 4 randomized studies including 276 patients of the use of rituximab for treatment of Sjogren syndrome and concluded that there is moderate-quality evidence that a single course of therapy improves lacrimal function and low-quality evidence of a potential improvement in salivary flow; however, rituximab was not observed to have any incremental benefit on overall disease activity, quality of life, oral dryness, or fatigue reduction.(50) **(EG 1)** Specialty consensus guidelines and review articles noted conflicting results in studies with rituximab and concluded that rituximab may be useful for treating some systemic manifestations of primary Sjogren syndrome.(51)(52)(53)(54)(55) **(EG 2)**

For systemic lupus erythematosus, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review and meta-analysis of 31 studies (1112 patients) evaluating the efficacy of rituximab for treatment of refractory systemic lupus erythematosus found that rituximab was associated with decreased Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and British Isles Lupus Activity Group (BILAG) index scores, decreased glucocorticoid usage, and improved proteinuria; overall global, complete, and partial response rates were 72%, 46%, and 32%, respectively. However, the authors noted that heterogeneity in the outcome measures and doses and regimens of rituximab used among the included studies limited the results, and further randomized trials were recommended.(56) **(EG 1)** A systematic review evaluating biologic treatments for childhood-onset systemic lupus erythematosus found no randomized controlled trials evaluating rituximab and recommended future studies to fully understand its efficacy in this population.(57) **(EG 1)** A specialty society practice guideline states that rituximab can be considered for treatment of organ-threatening disease that is refractory to standard immunosuppressive therapy.(58) **(EG 2)** A phase III randomized trial of 292 patients with active systemic lupus erythematosus compared treatment with belimumab combined with either rituximab or placebo (while tapering other immunosuppressants and glucocorticoids) and found, at 52-week follow-up, no difference in disease control rates between the groups.(59) **(EG 1)** For nephritis due to systemic lupus erythematosus, a randomized double-blind placebo-controlled trial of 144 patients (Lupus Nephritis Assessment with Rituximab, or LUNAR) reported that the addition of rituximab to mycophenolate mofetil and corticosteroids did not improve clinical outcomes after 1 year of treatment; however, the authors acknowledged that the study was underpowered to detect a difference in partial rather than complete response.(60) **(EG 1)** Expert consensus guidelines and review articles state that, while formal evidence of effectiveness of rituximab in lupus nephritis is lacking, there is observational-level evidence of some efficacy, and rituximab use may be helpful in, and should be limited to, severely

refractory patients.(61)(62)(63)(64)(65) **(EG 2)** For pediatric systemic lupus erythematosus, a systematic review of 12 case series (272 pediatric patients) evaluating the efficacy of rituximab for the treatment of pediatric systemic lupus erythematosus found improvement in global disease activity (measured by various disease indices) and a steroid-sparing effect, but conflicting results with regard to specific disease manifestations (improvement in renal, neuropsychiatric, hematologic, and immunologic (double-stranded DNA) manifestations, with no effect on arthralgia, mucocutaneous lesions, or photosensitivity). However, the authors noted that none of the included studies were randomized, and prospective trials were recommended.(66) **(EG 1)**

For systemic sclerosis, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review and meta-analysis of 14 studies (597 patients) evaluating the efficacy of rituximab for treatment of systemic sclerosis found that rituximab was associated with improved modified Rodnan skin scores compared with conventional therapy, with no differences in pulmonary metrics (forced vital capacity and diffusing capacity of the lungs for carbon monoxide (DLCO)) seen between the groups. However, the authors noted that the lack of control arms in several included studies and heterogeneity among patients and concomitant treatments limited the results, and larger randomized trials were recommended.(67) **(EG 1)** A systematic review and meta-analysis of 3 randomized controlled trials (84 patients) evaluating rituximab treatment for systemic sclerosis-associated interstitial lung disease found, at 24-week to 48-week follow-up, very low-quality evidence that rituximab was associated with improved mean change in percent predicted forced vital capacity and modified Rodnan skin scores and no difference in DLCO compared with placebo treatment. The authors noted that the results were limited by significant study heterogeneity and the lack of interstitial lung disease as an a priori criterion in the included studies and recommended future studies to fully evaluate rituximab in this population, especially in patients with progressive disease despite alternative treatments.(68) **(EG 1)** An observational cohort study of 9829 patients with systemic sclerosis (254 of whom were treated with rituximab) found, at a median follow-up of 24.3 months, that rituximab was associated with improvement in skin fibrosis (defined as 25% improvement in modified Rodnan skin score) and number of patients decreasing or stopping steroids; no difference in forced vital capacity or DLCO was seen between cohorts. However, the authors noted that variability in rituximab regimens and the relatively short follow-up limited the results.(69) **(EG 2)** A specialty society guideline notes that rituximab should be considered as treatment for skin fibrosis or interstitial lung disease manifestations of systemic sclerosis but notes that further studies are recommended to understand the best timing and combinations of immune-targeted regimens.(70) **(EG 2)** Other specialty society guidelines note that mycophenolate mofetil is the first-line treatment for systemic sclerosis-associated interstitial lung disease, but rituximab can be considered as an alternative, though one guideline notes that supportive evidence for rituximab treatment is of very low quality.(71)(72) **(EG 2)** A review article notes that rituximab could be an option for treatment of refractory arthritis in patients with systemic sclerosis, though the recommendation is based on expert opinion and observational studies only.(73) **(EG 2)**

For thyroid eye disease (Graves orbitopathy), evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review and meta-analysis of 4 randomized controlled trials (293 patients) evaluating rituximab for the treatment of moderate to severe thyroid eye disease (Graves orbitopathy) found, at 24-week follow-up, that rituximab was associated with improved clinical activity scores and an insignificant improvement in proptosis compared with glucocorticoids. The incidence of adverse events varied among the included trials, and the authors recommended additional, larger prospective trials.(74) **(EG 1)**

Rationale

Use of this MCG care guideline helps the clinician determine if a particular treatment, medication, or service might be appropriate for a specific patient, taking into account their unique health complexities.

Use of these evidence-based clinical criteria to support decision making benefits the patient by identifying patient-specific complex clinical factors and conditions, promoting personalized treatment. Utilizing evidence-based clinical criteria promotes patient safety by helping ensure that potential patient benefits outweigh the risks. In addition, the use of evidence-based guidelines can increase consistency in treatment thresholds, leading to less variation in care and promoting equitable treatment among patients.

Related CMS Coverage Guidance

This guideline supplements but does not replace, modify, or supersede existing Medicare regulations or applicable National Coverage Determinations (NCDs) or Local Coverage Determinations (LCDs).

Code of Federal Regulations (CFR): 42 CFR 419.22(212); 42 CFR 422.101(213)

Internet-Only Manual (IOM) Citations: CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 14 - Medical Devices(214); CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 15 - Covered Medical and Other Health Services(215); CMS IOM Publication 100-02, Medicare Benefit Policy Manual, Chapter 16 - General Exclusions from Coverage(216)

Medicare Coverage Determinations: Medicare Coverage Database(217)

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Footnotes

[A] For the treatment of chronic lymphocytic leukemia, CBC and platelet count should be regularly monitored during and after rituximab therapy.(1) If a patient is hepatitis B surface antigen positive, concomitant antiviral therapy (eg, entecavir) is recommended.(103) [A in Context Link 1]

[B] If a patient receiving rituximab therapy for non-Hodgkin lymphoma is hepatitis B surface antigen positive, concomitant antiviral therapy (eg, entecavir) is recommended.(128) [B in Context Link 1, 2]

[C] For non-Hodgkin lymphoma, partial response is defined as regression of measurable disease and absence of disease at new sites.(128) [C in Context Link 1]

[D] For diffuse large B-cell disease, CBC and platelet count should be regularly monitored during and after therapy with rituximab.(1) [D in Context Link 1]

[E] Rheumatoid arthritis disease activity should be evaluated by a validated tool that assesses disease severity; validated disease activity tools typically include a combination of patient self-assessment, physical examination of joints by a physician, and laboratory assessment of inflammatory response. An expert consensus recommendation supports use of the following instruments: the Clinical Disease Activity Index, the Disease Activity Score using 28-joint counts, the Patient Activity Scale-II, the Routine Assessment of Patient Index Data 3, and the Simplified Disease Activity Index.(193) [E in Context Link 1]

[F] The Clinical Disease Activity Index is a scale from 0 to 76 that uses physician joint count and both patient and physician global score to assess rheumatoid arthritis disease severity. A score of 2.8 or less indicates remission, while a score greater than 2.8 to 10 indicates low disease severity. Moderate disease activity is indicated by a score of greater than 10 to 22, and severe disease activity is indicated by a score of greater than 22.(194) [F in Context Link 1]

[G] The Disease Activity Score using 28-joint counts (DAS28) is a scale from 0 to 9.4 that is calculated by counting affected joints, the patient global score, and either the erythrocyte sedimentation rate or C-reactive protein level. A score of less than 2.6 indicates remission, while a score of 2.6 to less than 3.2 demonstrates low disease activity. Moderate disease activity is indicated by a score of 3.2 to 5.1, and severe disease activity is indicated by a score higher than 5.1.(194) [G in Context Link 1]

[H] The Patient Activity Scale and Patient Activity Scale-II consist of scales from 0 to 10 and use health assessment questionnaires to determine disease severity; they do not utilize affected joint counts or laboratory results. A score of 0.25 or less indicates remission. Low-severity disease is represented by a score of 0.26 to 3.7, and moderate disease activity is indicated by a score of 3.71 to less than 8. Severe disease activity is indicated by a score of 8 to 10.(194) [H in Context Link 1]

[I] The Routine Assessment of Patient Index Data 3 is a scale from 0 to 30 that is commonly used in clinical practice and uses a health assessment questionnaire and a patient global score to determine disease severity; it does not require joint counts or laboratory results. A score of 3 or less indicates remission. Low-severity disease is represented by a score of 4 to 6, and moderate disease activity is indicated by a score of 7 to 12. Severe disease activity is indicated by a score of 13 or greater.(194) [I in Context Link 1]

[J] The Simplified Disease Activity Index is a scale from 0 to 86 and is calculated by counting affected joints, the patient and provider global score, and the C-reactive protein level. A score of 3.3 or less indicates remission, while a score greater than 3.3 to 11 indicates low disease activity. Moderate disease activity is indicated by a score greater than 11 to 26, and severe disease activity is indicated by a score higher than 26.(194) [J in Context Link 1]

[K] For Waldenstrom macroglobulinemia, complete response is categorized by all of the following: disappearance of serum and urine monoclonal protein by immunofixation, absence of malignant cells in bone marrow histology, resolution of adenopathy/organomegaly by CT scan, and no signs or symptoms attributable to Waldenstrom macroglobulinemia.(198)(208) [K in Context Link 1]

Codes

HCPCS: J9311, J9312

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