Clinical Policy: Rituximab (Rituxan)
Reference Number: ERX.SPMN.154
Effective Date: 10/16
Last Review Date: 09/16

See Important Reminder at the end of this policy for important regulatory and legal information.

Policy/Criteria
It is the policy of health plans affiliated with Envolve Pharmacy Solutions® that rituximab (Rituxan®) is medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Non-Hodgkin’s Lymphoma (must meet all):
      1. Diagnosis of non-Hodgkin’s lymphoma (NHL);
      2. Member meets a or b:
         a. FDA approved use:
            i. Rituxan will be used in one of the following ways for CD20-positive, B-cell NHL:
               a) As a single agent for:
                  1) Relapsed or refractory disease;
                  2) Low-grade or follicular disease;
               b) In combination with first line chemotherapy for initial treatment;
               c) As a single-agent maintenance therapy in members achieving a complete or partial response to Rituxan in combination with chemotherapy;
               d) As a single-agent after first-line CVP chemotherapy for disease that is non-progressing (including stable disease);
               e) In combination with CHOP or other anthracycline-based chemotherapy regimens for diffuse large B-cell disease;
         b. NCCN recommended use for NHL subtypes and associated disorders:
            i. Chronic lymphocytic leukemia/small lymphocytic lymphoma;
            ii. Follicular lymphoma;
            iii. Marginal zone lymphomas;
               a) Gastric MALT lymphoma;
               b) Nongastric MALT lymphoma;
               c) Splenic marginal zone lymphoma;
            iv. Mantle cell lymphoma;
            v. Diffuse large B-cell lymphoma;
            vi. Burkitt lymphoma;
            vii. Lymphoblastic lymphoma;
            viii AIDS-related B-cell lymphoma;
            ix. Hairy cell leukemia;
            x. Primary cutaneous B-cell lymphoma;
            xi. Post-transplant lymphoproliferative disorder;
            xii. Castleman’s disease;
            xiii Waldenström’s macroglobulinemia/lymphoplasmacytic lymphoma.
CLINICAL POLICY
Rituximab

Approval duration: 3 months
B. Chronic Lymphocytic Leukemia (must meet all):
   1. Diagnosis of CD20-positive, chronic lymphocytic leukemia (CLL);
   2. Rituxan will be used in combination with fludarabine and cyclophosphamide.

Approval duration: 3 months

C. Rheumatoid Arthritis (must meet all):
   1. Prescribed by or in consultation with a rheumatologist;
   2. Age ≥ 18 years;
   3. Diagnosis of rheumatoid arthritis (RA) and one or more of the following:
      a. At least five inflamed joints;
      b. Elevation in the erythrocyte sedimentation rate (ESR) and/or serum C-reactive protein (CRP) concentration;
      c. Positive rheumatoid factor and/or anticyclic citrullinated peptide (CCP) antibodies (present in most patients);
      d. Evidence of inflammation on plain radiography of the hands, wrists, or feet, such as osteopenia and/or periarticular swelling;
   4. Member has failed one of the following therapies, unless contraindicated:
      a. A biologic for RA other than Rituximab;
      b. Methotrexate (MTX) for ≥ 3 consecutive months;
      c. If MTX is contraindicated, sulfasalazine or leflunomide for ≥ 3 consecutive months;
   5. Member has failed Enbrel AND Humira, each trialed for ≥ 3 consecutive months, unless contraindicated;
   6. Rituxan will be administered in combination with MTX unless contraindicated;
   7. Prescribed dosage regimen of Rituxan does not exceed two-1000 mg intravenous (IV) infusions separated by 2 weeks, then subsequent courses no more frequent than every 16 weeks.

Approval duration: 6 months

D. Granulomatosis with Polyangiitis (Wegener’s Granulomatosis) and Microscopic Polyangiitis (must meet all):
   1. Prescribed by or in consultation with a rheumatologist;
   2. Age ≥ 18 years;
   3. Diagnosis of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA);
   4. Rituxan will be administered in combination with glucocorticoid therapy;
   5. Prescribed frequency of Rituxan does not exceed once weekly.

Approval duration: 4 weeks total

E. Other diagnoses/indications: Refer to ERX.SPMN.16 - Global Biopharm Policy.
1. Additional off-label NCCN compendial uses for rituximab, meeting NCCN categories 1, 2a or 2b, are approved for the following indications per the USS.SPMN.16 Global Biopharm policy:
   a. Acute lymphoblastic leukemia;
   b. Central nervous system (CNS) cancers:
      i. Leptomeningeal metastases from lymphomas (intrathecal administration);
      ii. Primary CNS lymphoma;

II. Continued Approval
A. All Indications (must meet all):
   1. Currently receiving medication via health plan benefit or member has previously met all initial approval criteria;
   2. Member is compliant and responding positively to therapy;
   3. Prescribed regimen does not exceed the following:
      a. For RA: 1000 mg IV infusions no more frequency than every 16 weeks;
      b. For GPA and MPA: once weekly IV infusions (not to exceed 4 total infusion).

Approval duration:
12 months (6 months for NHL and CLL, up to 4 weeks total for GPA/MPA)

B. Other diagnoses/indications (must meet 1 or 2):
   1. Currently receiving medication via health plan benefit and documentation supports positive response to therapy; or
   2. Refer to ERX.SPMN.16 - Global Biopharm Policy.

Background
Description/Mechanism of Action:
Rituxan (rituximab) is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Rituximab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab mediates B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). The antibody induced apoptosis in the DHL 4 human B cell lymphoma cell line. B cells are believed to play a role in the pathogenesis of rheumatoid arthritis (RA) and associated chronic synovitis. In this setting, B cells may be acting at multiple sites in the autoimmune/inflammatory process, including through production of rheumatoid factor (RF) and other autoantibodies, antigen presentation, T-cell activation, and/or proinflammatory cytokine production.

Formulations:
Rituxan is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituxan is supplied at a concentration of 10 mg/mL in either 100
Rituximab is a CD20-directed cytolytic antibody indicated for the treatment of patients with:

- **Non-Hodgkin's lymphoma:**
  - Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent.
  - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to Rituxan in combination with chemotherapy, as single-agent maintenance therapy.
  - Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy.
  - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens.

- **Chronic lymphocytic leukemia:**
  - Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC).

- **Rheumatoid arthritis:**
  - Moderately- to severely- active rheumatoid arthritis in adult patients in combination with methotrexate and after inadequate response to one or more TNF antagonist therapies.

- **Granulomatosis with polyangiitis (Wegener’s granulomatosis) and microscopic polyangiitis:**
  - GPA and MPA in adult patients in combination with glucocorticoids.

Limitations of use:
- Rituxan is not recommended for use in patients with severe, active infections.

**Appendices**

**Appendix A: Abbreviation Key**

- ADCC: antibody dependent cell mediated cytotoxicity
- CDC: complement dependent cytotoxicity
- CLL: chronic lymphocytic leukemia
- CRP: C-reactive protein
- DMARD: disease-modifying antirheumatic drug
- ESR: elevation in the erythrocyte sedimentation rate
- GPA: granulomatosis with polyangiitis (Wegener’s granulomatosis)
- MPA: microscopic polyangiitis
- MTX: methotrexate
- NSAID: non-steroidal anti-inflammatory drug
- PML: progressive multifocal leukoencephalopathy
- RA: rheumatoid arthritis
- TNF: tumor necrosis factor
Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

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<th>HCPCS Codes</th>
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<td>Injection, rituximab, 100 mg</td>
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Reviews, Revisions, and Approvals

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Policy split from USS.SPMN.44 Rheumatoid Arthritis and Ankylosing Spondylitis Treatments and converted to new template. All safety criteria removed. Added dosing. RA: added age requirement; added requirement for trial and failure of PDL Enbrel and Humira, unless contraindicated; if the former are contraindicated, to require trial of methotrexate; if the former is contraindicated, added sulfasalazine as an alternative. In addition to RA, all other FDA-approved indications are added as well as NCCN compendia uses. Re-auth: combined into All Indications; added dosing and reasons to discontinue. Approval durations are 3 and 6 months for oncology and 6 and 12 months for all other indications.

References

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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