Rituximab

**Description**

Rituxan (rituximab), Truxima* (rituximab-abbs)

*These medications are included in this policy but are not available in the market as of yet

**Background**

Rituxan and its biosimilar are monoclonal antibodies that are manufactured through biotechnology methods rather than by the human body’s own immune system. The drugs work by greatly reducing the number of specific immune cells in the blood, known as B-cells. The drugs bind to a particular protein, the CD20 antigen, on the surface of normal and malignant B-cells, making it easier for the patient’s immune system to attack the cancer cell as if it were a foreign pathogen. The targeted mechanism of action of Rituxan and its biosimilar are used in the treatment of the following: chronic lymphocytic leukemia (CLL), CD20 positive, Non-Hodgkin’s Lymphoma (NHL), rheumatoid arthritis (RA), Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis), Microscopic Polyangiitis (MPA) and active pemphigus vulgaris (1-5).

**Regulatory Status**

FDA-approved indication: Rituxan and its biosimilar are CD20-directed cytolytic antibodies indicated for the treatment of patients with: (1-2)

1. Non-Hodgkin’s Lymphoma (NHL)
2. Chronic lymphocytic leukemia (CLL)
3. Rheumatoid arthritis (RA) in combination with methotrexate in adult patients with moderately- to severely-active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.
4. Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA) in combination with glucocorticoids.

5. Moderately to severely active pemphigus vulgaris (PV)

**Limitations of use:**
Rituxan and its biosimilar are not recommended for use in patients with severe, active infections (1-2).

Rituxan and its biosimilar have several boxed warnings regarding fatal infusion reactions, tumor lysis syndrome (TLS), severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy (PML) resulting in death (1-2).

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12-24 hours after the first infusion of Rituxan or its biosimilar in patients with non-Hodgkin lymphoma (NHL). Patients at high risk for tumor lysis syndrome should be administered aggressive intravenous hydration, anti-hyperuricemic agents, and their renal function should be monitored (1-2).

Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of therapy of Rituxan or its biosimilar. Discontinue Rituxan or its biosimilar for serious infections and institute appropriate anti-infective therapy (1-2).

Rituxan and its biosimilar should be discontinued in patients that develop serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of Rituxan or its biosimilar for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina (1-2).

The safety of immunization with live viral vaccines following Rituxan and its biosimilar therapy have not been studied and vaccination with live virus vaccines is not recommended (1-2).

In patients with lymphoid malignancies, during treatment with Rituxan or its biosimilar monotherapy, obtain complete blood counts (CBC) and platelet counts prior to each rituximab course. During treatment with Rituxan or its biosimilar in combination with chemotherapy, obtain CBC and platelet counts at weekly to monthly intervals and more frequently in patients who develop cytopenias. In patients with rheumatoid arthritis, granulomatosis with polyangiitis (GPA), or microscopic polyangiitis (MPA), obtain CBC and platelet counts at two to four month
intervals during rituximab therapy. The duration of cytopenias caused by Rituxan or its biosimilar can extend months beyond the treatment period (1-2).

**Off Label Uses:**
There are a number of important off-label uses for the use of Rituxan (rituximab) and its biosimilar that are supported by the medical literature. The inclusion of the following conditions is based on the studies cited.

**Other Non-Hodgkin’s Lymphomas**
1. Burkitt lymphoma
2. Gastric MALT lymphoma
3. Non-gastric MALT lymphoma
4. Nodal Marginal Zone lymphoma
5. Mantle cell lymphoma
6. AIDS-Related B-cell lymphomas
7. Post-transplant lymphoproliferative disorder
8. Primary cutaneous B-cell lymphoma
9. Splenic marginal zone lymphoma
10. Hairy Cell Leukemia
11. Castleman’s disease

**Other Conditions**
1. Waldenström’s macroglobulinemia
2. Steroid refractory chronic graft vs. host disease
3. Immune thrombocytopenic purpura
4. Thrombotic thrombocytopenic purpura
5. Refractory autoimmune hemolytic anemia
6. Leptomeningeal metastases
7. Primary central nervous system lymphoma
8. Hodgkin’s lymphoma

Rituxan or its biosimilar as monotherapy or in conjunction with various chemotherapy agents as well as other monoclonal antibodies is supported by clinical trial data and NCCN guideline recommendations. The following chemoimmunotherapy regimens are used for either first-line therapy or relapsed/refractory therapy depending on the results of genetic testing and comorbidities in affected patients: (6)
1. Alemtuzumab + rituximab
2. Bendamustine, rituximab (BR)
3. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
4. HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab
5. Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab
6. HDMP (high-dose methylprednisolone) + rituximab
7. Pentostatin, cyclophosphamide, rituximab (PCR)
8. CFAR (cyclophosphamide, fludarabine, alemtuzumab, rituximab)
9. OFAR (oxaliplatin, fludarabine, cytarabine, rituximab)
10. Lenalidomide + rituximab

Related policies
Actemra, Arzerra, Cablivi, Cimzia, Enbrel, Gazyva, Humira, Infliximab, Kevzara, Kineret, Olumiant, Orencia, Rituxan Hycela, Simponi, Xeljanz

Policy
This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Rituxan and its biosimilar may be considered medically necessary in patients 18 years of age or older for the treatment of Non-Hodgkin's Lymphoma, B-Cell, CD20-Positive, which include Chronic Lymphocytic Leukemia, follicular lymphoma, diffuse large B-cell lymphoma, Burkitt lymphoma, gastric MALT lymphoma, non-gastric MALT lymphoma, nodal marginal zone lymphoma, mantle cell lymphoma, AIDS-Related B-cell lymphomas, post-transplant lymphoproliferative disorder, primary cutaneous B-cell lymphoma, splenic marginal zone lymphoma, hairy cell leukemia or Castleman’s disease, rheumatoid arthritis, granulomatosis with polyangiitis (formerly Wegener's granulomatosis), microscopic polyangiitis, Waldenström’s macroglobulinemia, steroid refractory chronic graft vs. host disease, immune thrombocytopenic purpura, thrombotic thrombocytopenic purpura, refractory autoimmune hemolytic anemia, leptomeningeal metastases, primary central nervous system lymphoma, Hodgkin’s lymphoma, or pemphigus vulgaris (PV) and if the conditions indicated below are met.

Rituxan and its biosimilar may be considered investigational in patients less than 18 years of age and for all other indications.

Prior-Approval Requirements
Age 18 years of age or older

Diagnoses

Patient must have ONE of the following:

1. Non-Hodgkin Lymphomas (NHL), B-Cell, CD20-Positive with ONE of the following indications:
   a. Follicular lymphoma
   b. Diffuse large B-cell lymphoma
   c. Burkitt lymphoma
   d. Gastric MALT lymphoma
   e. Non-gastric MALT lymphoma
   f. Nodal Marginal Zone lymphoma
   g. Mantle cell lymphoma
   h. AIDS-Related B-cell lymphomas
   i. Post-transplant lymphoproliferative disorder
   j. Primary cutaneous B-cell lymphoma
   k. Splenic marginal zone lymphoma
   l. Hairy Cell Leukemia
   m. Castleman’s disease

2. Chronic Lymphocytic Leukemia (CLL)

3. Rheumatoid arthritis (RA)
   a. Moderately- to severely-active RA
   b. Inadequate treatment response, intolerance, or contraindication to one or more tumor necrosis factor (TNF) antagonist therapies

4. Microscopic polyangiitis (MPA)
   a. Currently taking a glucocorticoid

5. Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)
   a. Currently taking a glucocorticoid

6. Waldenström’s macroglobulinemia

7. Steroid refractory chronic graft vs. host disease

8. Immune thrombocytopenic purpura

9. Thrombotic thrombocytopenic purpura

10. Refractory autoimmune hemolytic anemia

11. Leptomeningeal metastases

12. Primary central nervous system lymphoma

13. Hodgkin’s lymphoma
14. Moderately to severely active pemphigus vulgaris (PV)

AND NONE of the following for ALL indications:
   a. Used in combination with any other biologic DMARD or targeted synthetic DMARD
   b. Use of live vaccines (Non-live vaccines should be administered at 4 weeks prior to a course of rituximab)
   c. Active bacterial, invasive fungal, viral, and other opportunistic infections

Prior – Approval Renewal Requirements

Age 18 years of age or older

Diagnoses

Patient must have ONE of the following:

1. Non-Hodgkin Lymphomas (NHL), B-Cell, CD20-Positive with ONE of the following indications:
   a. Follicular lymphoma
   b. Diffuse large B-cell lymphoma
   c. Burkitt lymphoma
   d. Gastric MALT lymphoma
   e. Non-gastric MALT lymphoma
   f. Nodal Marginal Zone lymphoma
   g. Mantle cell lymphoma
   h. AIDS-Related B-cell lymphomas
   i. Post-transplant lymphoproliferative disorder
   j. Primary cutaneous B-cell lymphoma
   k. Splenic marginal zone lymphoma
   l. Hairy Cell Leukemia
   m. Castleman’s disease

2. Chronic Lymphocytic Leukemia (CLL)
3. Rheumatoid arthritis (RA)
4. Microscopic polyangiitis (MPA)
   a. Currently taking a glucocorticoid
5. Granulomatosis with polyangiitis (formerly Wegener’s granulomatosis)
a. Currently taking a glucocorticoid
6. Waldenström’s macroglobulinemia
7. Steroid refractory chronic graft vs. host disease
8. Immune thrombocytopenic purpura
9. Thrombotic thrombocytopenic purpura
10. Refractory autoimmune hemolytic anemia
11. Leptomeningeal metastases
12. Primary central nervous system lymphoma
13. Hodgkin’s lymphoma
14. Pemphigus vulgaris (PV)

AND NONE of the following for ALL indications:
   a. Used in combination with any other biologic DMARD or targeted synthetic DMARD
   b. Use of live vaccines (Non-live vaccines should be administered at 4 weeks prior to a course of rituximab)
   c. Active bacterial, invasive fungal, viral, and other opportunistic infections

**Policy Guidelines**

**Pre - PA Allowance**
None

**Prior - Approval Limits**
**Duration** 12 months

**Prior – Approval Renewal Limits**
**Duration** 12 months

**Rationale**

**Summary**
Rituxan and its biosimilar are monoclonal antibodies that are manufactured through biotechnology methods rather than by the human body’s own immune system. The drugs work by greatly reducing the number of specific immune cells in the blood, known as B-cells. The drugs bind to a particular protein, the CD20 antigen, on the surface of normal and malignant B-cells, making it easier for the patient’s immune system to attack the cancer cell as if it were a
foreign pathogen. Rituxan and its biosimilar are therefore used to treat diseases which are characterized by excessive numbers of B cells, overactive B cells, or dysfunctional B cells. This includes non-hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), rheumatoid arthritis (RA), microscopic polyangiitis (MPA), granulomatosis with polyangiitis, and pemphigus vulgaris (PV) (1-5).

Prior authorization is required to ensure the safe, clinically appropriate and cost effective use of Rituxan (rituximab) and its biosimilar while maintaining optimal therapeutic outcomes.

References
### Prescription Drugs

**Effective Date:** July 1, 2019

**Original Policy Date:** July 29, 2011

**Subject:** Rituximab

#### Date

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>February 2012</td>
<td>Added Methotrexate (MTX) is required unless there is intolerance to MTX, contraindication to MTX or failure on MTX.</td>
</tr>
<tr>
<td>September 2012</td>
<td>Annual editorial and reference update</td>
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<tr>
<td></td>
<td>Deleted requirement of concurrent fludarabine and cyclophosphamide therapy for CLL (NCCN guidelines include many other concurrent therapies)</td>
</tr>
<tr>
<td>December 2012</td>
<td>Added indication for thrombotic thrombocytopenic purpura.</td>
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<tr>
<td>March 2013</td>
<td>Added exclusion of concomitant TNFI therapy or other biologic DMARD</td>
</tr>
<tr>
<td></td>
<td>Added exclusion of live vaccine within two weeks.</td>
</tr>
<tr>
<td>September 2013</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
<td>March 2014</td>
<td>Annual editorial review</td>
</tr>
<tr>
<td>September 2014</td>
<td>Annual editorial review</td>
</tr>
<tr>
<td>December 2014</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
<td>March 2015</td>
<td>Addition of Revlimid (lenalidomide) to combination therapy and defined NHL categories</td>
</tr>
<tr>
<td>June 2015</td>
<td>Annual review</td>
</tr>
<tr>
<td>December 2015</td>
<td>Annual review and reference update</td>
</tr>
<tr>
<td></td>
<td>Revised RA statement: Inadequate treatment response, intolerance, or contraindication to one or more tumor necrosis factor (TNF) antagonist therapies</td>
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<tr>
<td>June 2016</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
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<td>Change of NOT using a Tumor Necrosis Factor (TNF) antagonist and NOT using any of the following: Abatacept (Orencia),Tocilizumab (Actemra), Anakinra (Kineret), Tofacitinib (Xeljanz) to not to be used in combination with any other biologic DMARD or targeted synthetic DMARD</td>
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<td></td>
<td>Addition of indications: leptomeningeal metastases, primary central nervous system lymphoma, Hodgkin’s lymphoma and Castleman’s disease</td>
</tr>
<tr>
<td>June 2017</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
<td></td>
<td>Addition of the age requirement to all indications</td>
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<tr>
<td>December 2017</td>
<td>Annual Editorial review</td>
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<tr>
<td></td>
<td>Updated renewal section</td>
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<tr>
<td>June 2018</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
<td>July 2018</td>
<td>Addition of pemphigus vulgaris (PV) diagnosis to criteria, revised active infection criteria statement</td>
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<tr>
<td>September 2018</td>
<td>Annual editorial review</td>
</tr>
<tr>
<td>December 2018</td>
<td>Addition of biosimilar Truxima. Changed policy name to Rituximab</td>
</tr>
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<td>March 2019</td>
<td>Annual review and reference update</td>
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Section: Prescription Drugs  
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Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 20, 2019 and is effective on July 1, 2019.