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5.21.010

Section:	Prescription Drugs	**Effective Date:**	April 1, 2024
Subsection:	Antineoplastic Agents	**Original Policy Date:**	July 29, 2011
Subject:	Rituximab	**Page:**	1 of 14

Last Review Date: March 8, 2024

Rituximab

Description

Rituxan (rituximab), **Riabni** (rituximab-arrx), Ruxience (rituximab-pvvr), Truxima (rituximab-abbs)

Preferred products: Riabni, Rituxan

Background
Rituxan (rituximab) and its biosimilars 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 biosimilars 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 (1-7).

Regulatory Status
FDA-approved indications: Rituxan and its biosimilars are CD20-directed cytolytic antibodies indicated for the treatment of patients with: (1-4)

1. Adult patients with Non-Hodgkin's Lymphoma (NHL)
2. Pediatric patients aged 6 months and older with mature B-cell Non-Hodgkin's Lymphoma (NHL) and mature B-cell acute leukemia

   a. Diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, Burkitt-like lymphoma, or mature B-cell acute leukemia
3. Adult patients with Chronic lymphocytic leukemia (CLL)
4. 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
5. Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult and pediatric patients 2 years of age and older in combination with glucocorticoids.
6. Moderately to severely active pemphigus vulgaris (PV) in adult patients

Limitations of Use:
Rituxan and its biosimilars are not recommended for use in patients with severe, active infections (1-4).

Rituxan and its biosimilars have several boxed warnings regarding fatal infusion reactions, Hepatitis B virus (HBV) reactivation, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy (PML) resulting in death (1-4).

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 biosimilars 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 (1-4).

Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of therapy of Rituxan or its biosimilars. Discontinue Rituxan or its biosimilars for serious infections and institute appropriate anti-infective therapy (1-4).

Rituxan and its biosimilars 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 biosimilars for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina (1-4).

The safety of immunization with live viral vaccines following Rituxan and its biosimilars have not been studied and vaccination with live virus vaccines is not recommended (1-4).

In patients with lymphoid malignancies, during treatment with Rituxan or its biosimilars as monotherapy, obtain complete blood counts (CBC) and platelet counts prior to each rituximab course. During treatment with Rituxan or its biosimilars 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 biosimilars can extend months beyond the treatment period (1-4).

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

Other Non-Hodgkin's Lymphomas (5)

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 (5-12)

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
9. Refractory systemic lupus erythematosus (SLE)
10. Refractory myasthenia gravis (MG)

Rituxan or its biosimilars 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: (5)

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 methylpredisolone) + rituximab
7. Pentostatin, cyclophosphamide, rituximab) (PCR)
8. CFAR (cyclophosphamide, fludarabine, alemtuzumab, rituximab)
9. OFAR (oxaliplatin, fludarabine, cytarabine, rituximab)
10. Lenalidomide + rituximab

Related policies
Arzerra, Cablivi, Gazyva, Infliximab, Rituxan Hycela

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 biosimilars may be considered **medically necessary** if the conditions indicated below are met.

Rituxan and its biosimilars may be considered **investigational** 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 (DLBCL)
    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. Waldenström's macroglobulinemia
5. Steroid refractory chronic graft vs. host disease
6. Immune thrombocytopenic purpura
7. Thrombotic thrombocytopenic purpura
8. Refractory autoimmune hemolytic anemia
9. Leptomeningeal metastases
10. Primary central nervous system lymphoma
11. Hodgkin's lymphoma
12. Refractory systemic lupus erythematosus (SLE)
13. Refractory myasthenia gravis (MG)
    a. Inadequate treatment response, intolerance, or contraindication to at least **TWO** conventional therapies for MG (e.g., corticosteroids, azathioprine, mycophenolate, cyclosporine, methotrexate, tacrolimus, cyclophosphamide, etc.)
14. Moderately to severely active pemphigus vulgaris (PV)

AND ALL of the following for **ALL** indications:

a. **NOT** given concurrently with live vaccines (non-live vaccines should be administered at 4 weeks prior to a course of rituximab)
b. If the patient has a history of Hepatitis B (HBV) infection:
    i. Prescriber agrees to monitor for HBV reactivation
c. **NO** severe active infections
d. Prescriber agrees to monitor for signs of progressive multifocal leukoencephalopathy (PML) or severe mucocutaneous reactions
e. **NOT** used in combination with any other biologic DMARD or targeted synthetic DMARD (see Appendix 1)
f. **Non-preferred products only**: Inadequate treatment response, intolerance, or contraindication to **ONE** of the preferred products (Riabni, Rituxan, Rituxan Hycela)

Age 2 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Microscopic polyangiitis (MPA)
    a. Concurrent use with a glucocorticoid
2. Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)
    a. Concurrent use with a glucocorticoid

AND ALL of the following for **ALL** indications:

a. **NOT** given concurrently with live vaccines (non-live vaccines should be administered at 4 weeks prior to a course of rituximab)
b. If the patient has a history of Hepatitis B (HBV) infection:
    i. Prescriber agrees to monitor for HBV reactivation
c. **NO** severe active infections
d. Prescriber agrees to monitor for signs of progressive multifocal leukoencephalopathy (PML) or severe mucocutaneous reactions
e. **NOT** used in combination with any other biologic DMARD or targeted synthetic DMARD (see Appendix 1)
f. **Non-preferred products only**: Inadequate treatment response, intolerance, or contraindication to **ONE** of the preferred products (Riabni, Rituxan, Rituxan Hycela)

Age 6 months 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. Diffuse large B-cell lymphoma (DLBCL)
    b. Burkitt lymphoma
    c. Burkitt-like lymphoma
2. Mature B-cell acute leukemia

AND ALL of the following for **ALL** indications:

a. **NOT** given concurrently with live vaccines (non-live vaccines should be administered at 4 weeks prior to a course of rituximab)
b. If the patient has a history of Hepatitis B (HBV) infection:
    i. Prescriber agrees to monitor for HBV reactivation
c. **NO** severe active infections
d. Prescriber agrees to monitor for signs of progressive multifocal leukoencephalopathy (PML) or severe mucocutaneous reactions
e. **NOT** used in combination with any other biologic DMARD or targeted synthetic DMARD (see Appendix 1)
f. **Non-preferred products only**: Inadequate treatment response, intolerance or contraindication to **ONE** of the preferred products (Riabni, Rituxan, Rituxan Hycela)

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. Waldenström's macroglobulinemia
5. Steroid refractory chronic graft vs. host disease
6. Immune thrombocytopenic purpura
7. Thrombotic thrombocytopenic purpura
8. Refractory autoimmune hemolytic anemia
9. Leptomeningeal metastases
10. Primary central nervous system lymphoma
11. Hodgkin's lymphoma
12. Refractory systemic lupus erythematosus (SLE)
13. Refractory myasthenia gravis (MG)
14. Pemphigus vulgaris (PV)

AND ALL of the following for **ALL** indications:

a. **NOT** given concurrently with live vaccines (non-live vaccines should be administered at 4 weeks prior to a course of rituximab)
b. If the patient has a history of Hepatitis B (HBV) infection:
    i. Prescriber agrees to monitor for HBV reactivation
c. **NO** severe active infections
d. Prescriber agrees to monitor for signs of progressive multifocal leukoencephalopathy (PML) or severe mucocutaneous reactions
e. **NOT** used in combination with any other biologic DMARD or targeted synthetic DMARD (see Appendix 1)

Age 2 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Microscopic polyangiitis (MPA)
    a. Concurrent use with a glucocorticoid
2. Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)
    a. Concurrent use with a glucocorticoid

AND ALL of the following for **ALL** indications:

a. **NOT** given concurrently with live vaccines (non-live vaccines should be administered at 4 weeks prior to a course of rituximab)
b. If the patient has a history of Hepatitis B (HBV) infection:
    i. Prescriber agrees to monitor for HBV reactivation
c. **NO** severe active infections
d. Prescriber agrees to monitor for signs of progressive multifocal leukoencephalopathy (PML) or severe mucocutaneous reactions
e. **NOT** used in combination with any other biologic DMARD or targeted synthetic DMARD (see Appendix 1)

Age 6 months 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. Diffuse large B-cell lymphoma (DLBCL)
    b. Burkitt lymphoma
    c. Burkitt-like lymphoma
2. Mature B-cell acute leukemia

AND ALL of the following for **ALL** indications:

a. **NOT** given concurrently with live vaccines (non-live vaccines should be administered at 4 weeks prior to a course of rituximab)
b. If the patient has a history of Hepatitis B (HBV) infection:
    a. Prescriber agrees to monitor for HBV reactivation
c. **NO** severe active infections
d. Prescriber agrees to monitor for signs of progressive multifocal leukoencephalopathy (PML) or severe mucocutaneous reactions
e. **NOT** used in combination with any other biologic DMARD or targeted synthetic DMARD (see Appendix 1)

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Rituxan (rituximab) and its biosimilars 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 biosimilars are therefore used to treat diseases which are characterized by excessive numbers of B cells, overactive B cells, or dysfunctional B cells (1-6).

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

References

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12. Lebrun C, Bourg V, Tieulie N, et al: Successful treatment of refractory generalized myasthenia gravis with rituximab. Eur J Neurol 2009; 16(2):246-250.

Policy History

Date	Action
February 2012	Added Methotrexate (MTX) is required unless there is intolerance to MTX, contraindication to MTX or failure on MTX.
September 2012	Annual editorial and reference update Deleted requirement of concurrent fludarabine and cyclophosphamide therapy for CLL (NCCN guidelines include many other concurrent therapies)
December 2012	Added indication for thrombotic thrombocytopenic purpura.

March 2013	Added exclusion of concomitant TNFI therapy or other biologic DMARD Added exclusion of live vaccine within two weeks.
September 2013	Annual editorial review and reference update
March 2014	Annual editorial review
September 2014	Annual editorial review
December 2014	Annual editorial review and reference update
March 2015	Addition of Revlimid (lenalidomide) to combination therapy and defined NHL categories
June 2015	Annual review
December 2015	Annual review and reference update Revised RA statement: Inadequate treatment response, intolerance, or contraindication to one or more tumor necrosis factor (TNF) antagonist therapies
June 2016	Annual editorial review and reference update 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 Addition of indications: leptomeningeal metastases, primary central nervous system lymphoma, Hodgkin's lymphoma and Castleman's disease Policy number change from 5.04.10 to 5.21.10
June 2017	Annual editorial review and reference update Addition of the age requirement to all indications
December 2017	Annual Editorial review Updated renewal section
June 2018	Annual editorial review and reference update
July 2018	Addition of pemphigus vulargis (PV) diagnosis to criteria, revised active infection criteria statement
September 2018	Annual editorial review
December 2018	Addition of biosimilar Truxima. Changed policy name to Rituximab
March 2019	Annual review and reference update
June 2019	Annual review
August 2019	Addition of biosimilar Ruxience
September 2019	Annual review and reference update
October 2019	Age requirement reduced to 2 and older from 18 and older for granulomatosis with polyangiitis and microscopic polyangiitis with concurrent use with a glucocorticoid
December 2019	Annual review
March 2020	Annual review and reference update

June 2020	Annual review and reference update
December 2020	Added Truxima and Ruxience as preferred products. Added requirement for Rituxan to t/f the preferred products
January 2021	Addition of biosimilar Riabni
March 2021	Annual editorial review and reference update. Clarification added to the t/f, intolerance, C/I to preferred products requirement indicating that it only applies to claims adjudicated through the pharmacy benefit
June 2021	Annual review and reference update
December 2021	Annual review and reference update. Addition of off-label indication refractory systemic lupus erythematosus (SLE) per SME
January 2022	Addition of indication Non-Hodgkin's Lymphoma and mature B-cell acute leukemia in patients 6 months of age and older
March 2022	Annual review and reference update. Added Appendix 1
June 2022	Annual review and reference update
December 2022	Annual review and reference update. Changed policy number to 5.21.010
March 2023	Annual review and reference update. Per FEP, added off-label indication of refractory myasthenia gravis (MG)
June 2023	Annual review and reference update
December 2023	Annual review and reference update. Per FEP, changed preferred products to Rituxan, Rituxan Hycela, and Riabni. Also removed Medex requirements. Added t/f requirement of ONE preferred agent to initiation. Per SME, added requirements to monitor HBV reactivation and to monitor for PML. Also reworded no severe active infections requirement for consistency
March 2024	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 8, 2024 and is effective on April 1, 2024.

Appendix 1 - List of DMARDs

Biological disease-modifying antirheumatic drugs (DMARDs)

Generic Name	Brand Name
abatacept	Orencia
adalimumab	Humira
anakinra	Kineret
brodalumab	Siliq
certolizumab	Cimzia
etanercept	Enbrel
golimumab	Simponi/Simponi Aria
guselkumab	Tremfya
infliximab	Remicade/Avsola/Inflectra/Renflexis
ixekizumab	Taltz
risankizumab-rzaa	Skyrizi
rituximab	Rituxan/Riabni/Ruxience/Truxima
sarilumab	Kevzara
secukinumab	Cosentyx
spesolimab-sbzo	Spevigo
tildrakizumab-asmn	Ilumya
tocilizumab	Actemra
ustekinumab	Stelara
vedolizumab	Entyvio

Targeted synthetic disease-modifying antirheumatic drugs (DMARDs)

Generic Name	Brand Name
apremilast	Otezla
baricitinib	Olumiant
deucravacitinib	Sotyktu
tofacitinib	Xeljanz/XR
upadactinib	Rinvoq