Subject:	Rituximab Agents for Oncologic Indications Step Therapy		
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Overview

This document addresses step therapy for oncologic indications of rituximab products. Please refer to the following related clinical criteria for additional information

- ING-CC-0075 Rituximab Agents for Non-Oncologic Indications
- Rituxan Hycela (rituximab and hyaluronidase)

Rituxan and Biosimilar Products for Oncologic Indications

The reference product Rituxan (rituximab) is FDA approved for the treatment of CD20-positive Non-hodgkin's lymphomas (NHL) including relapsed/refractory low-grade or follicular NHL, previously untreated follicular lymphoma, non-progressing low-grade NHL, and previously untreated diffuse large B-cell lymphoma. NCCN defines low-grade lymphomas as follicular lymphoma and marginal zone lymphoma which includes Malt lymphomas and nodal/splenic type. Rituxan is also FDA approved to treat chronic lymphocytic leukemia (CLL) in combination with fludarabine and cyclophosphamide. Three biosimilars to Rituxan, Truxima (rituximab-abbs), Ruxience (rituximab-pvvr), and Riabni (rituximab-arrx) have been approved by the FDA. All three biosimilars have the same approved oncologic indications as Rituxan.

Biosimilar products must be highly similar to the reference product and there must be no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product. Biosimilars must utilize the same mechanism of action (MOA), route of administration, dosage form and strength as the reference product; and the indications proposed must have been previously approved for the reference product. The potential exists for a biosimilar product to be approved for one or more indications for which the reference product is licensed based on extrapolation of data intended to demonstrate biosimilarity in one indication. Sufficient scientific justification for extrapolating data is necessary for FDA approval. Factors and issues that should be considered for extrapolation include the MOA for each indication, the pharmacokinetics, bio-distribution, and immunogenicity of the product in different patient populations, and differences in expected toxicities in each indication and patient population.

Truxima was originally granted FDA approval in November of 2018 for the treatment of relapsed/refractory low grade or follicular NHL, previously untreated follicular NHL, and non-progressing low-grade NHL. Based on the totality of submitted data, the FDA concluded that Truxima is highly similar to Rituxan, there are no clinically meaningful differences between Truxima and Rituxan, and that there is justification to support licensure for the proposed indications. Clinical review of Truxima included 2 clinical studies that compared Truxima with Rituxan in the oncology setting. Both were randomized, double-blinded, parallel-group studies that enrolled subjects with either advanced follicular lymphoma or low tumor burden follicular lymphoma. Demonstration of biosimilarity was also based on a third study, a randomized, controlled, double-blind, 3-arm study of Truxima, US-Rituxan, and EU-approve MabThera in patients with rheumatoid arthritis (RA). In May of 2019, FDA granted Truxima approval for previously untreated DLBCL and previously untreated CLL. Ruxience was granted FDA approval for all the same oncologic indications as the reference product. Approval for Ruxience was, in part, based on a phase 3, randomized double-blind study of Ruxience versus MabThera in patients with low tumor burden follicular lymphoma (NCT02213263). Ruxience has also been studied in rheumatoid arthritis (Cohen 2018). Riabni was studied in two randomized, double blind studies with Rituxan as a comparator. Riabni demonstrated no difference in overall response rate in follicular lymphoma (Niederwieser 2020) and no difference in disease activity score change for rheumatoid arthritis (Burmester 2020). NCCN guideline on B-Cell Lymphomas recommends biosimilars as a substitute for Rituxan in all subtypes of B-cell Lymphomas. As Truxima, Ruxience, and Riabni have demonstrated biosimilarity to Rituxan for FDA indications, it is reasonable that biosimilarity can be extrapolated to off-label indications as well.

Rituximab products are used in defined treatment periods when used in oncologic indications. The package insert recommends that rituximab be used up to 2 years where it is indicated as maintenance therapy. As treatment periods are definite, NCCN notes that the biosimilar may be substituted for the reference product at the initiation of a course of treatment. Additionally, no biosimilar rituximab agent is approved as interchangeable, so the patient should remain on the same product that was used to initiate treatment during a single course of therapy. At this time, there is insufficient evidence for efficacy and safety of switching between the reference and biosimilar product in the treatment of oncologic indications.

Rituxan, Truxima, Ruxience, and Riabni have black box warnings for fatal infusion reactions, severe mucocutaneous reactions, hepatitis B virus (HBV) reactivation, and progressive multifocal leukoencephalopathy (PML). Rituximab administration can result in serious, including fatal, infusion reactions and deaths within 24 hours of infusion have occurred, most in association with the first infusion. Monitor individuals closely and discontinue rituximab infusion for severe reactions and provide medical treatment for grade 3 or 4 reactions. Severe, including fatal, mucocutaneous reactions can occur. HBV reactivation can occur and in some cases resulting in fulminant hepatitis, hepatic failure, and death. Screen all individuals for HBV infection before treatment initiation and monitor during and after treatment with rituximab. Discontinue rituximab and concomitant medications in the event of HBV reactivation. PML, including fatal PML, can occur.

Summary of FDA-approved and Off-label Oncologic Indications for Rituximab Products

	Rituxan (rituximab)	Truxima (rituximab-abbs)	Ruxience (rituximab-pvvr)	Riabni (rituximab-arrx)
Follicular Lymphoma	X	X	X	X
Gastric/nongastric malt Lymphoma	X/NCCN*	X/NCCN*	X/NCCN*	X/NCCN*
Nodal/Splenic Marginal Zone Lymphoma	X/NCCN*	X/NCCN*	X/NCCN*	X/NCCN*
Histologic transformation of marginal zone lymphoma to DLBCL	Y	Y	Y	Y
Post-transplant lymphoproliferative disorders	Y	Y	Y	Y
Castleman's disease	Y	Y	Y	Y
Mantle Cell lymphoma	Y	Y	Y	Y
DLBCL	X	X	X	X
High-Grade B-Cell lymphomas	Y	Y	Y	Y
Burkitt Lymphoma	Y	Y	Y	Y
AIDS-related B-cell Lymphomas	Y	Y	Y	Y
Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma	X	X	X	X
Primary Cutaneous B-Cell Lymphomas	Y	Y	Y	Y
Pediatric Aggressive Mature B-Cell Lymphomas	Y	Y^	Y^	Y^
Acute lymphoblastic Leukemia	Y	Y	Y	Y
Primary CNS Lymphoma	Y	Y	Y	Y
Leptomeningeal Metastases	Y	Y	Y	Y
Hairy Cell Leukemia	Y	Y	Y	Y
Histiocytic Neoplasms	Y	Y	Y	Y
Hodgkin Lymphoma	Y	Y	Y	Y
Waldenstrom Macroglobulinemia/ Lymphoplasmacytic Lymphoma	Y	Y	Y	Y

X= FDA approved use; Y= Off-label use; Y^= Off-label indication based on clinical judgement of biosimilarity by 3Q 2021 P&T committee
**NCCN defines low grade non-hodgkins lymphomas as MALT lymphoma and marginal zone lymphoma*

Step Therapy

Rituximab Reference and Biosimilar Agents for Oncologic Indications Step Therapy

Requests for a Rituxan (rituximab) for an oncologic indication may be approved when the following criteria are met:

I. Individual has had a trial and intolerance to one preferred agent;
Preferred agents: Ruxience, Truxima

OR

II. Individual is currently stabilized on Rituxan (rituximab).

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J9310	Injection, rituximab, 100 mg
Q5115	Injection, rituximab-abbs, biosimilar, (Truxima), 10 mg
Q5119	Injection, rituximab-pvvr, biosimilar, (RUXIENCE), 10 mg
Q5123	Injection, rituximab-arrx, biosimilar, (riabni), 10 mg [RIABNI™]

ICD-10 Diagnosis

C81.0-C84.4	Various Lymphoma diagnosis
C91.0-C91.5	Lymphoid Leukemias
D47.Z2	Castleman's Disease
C88.0	Waldenström macroglobulinemia

Document History

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- 09/20/2021 – New document for Louisiana Medicaid.

References

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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.