

<b>Subject: Rituxan™ (Rituximab)</b>	
<input type="checkbox"/> Original	<b>Original Committee Approval: October 13, 2006</b>
<input checked="" type="checkbox"/> Revised	<b>Last Committee Approval: December 3, 2008</b>
	<b>Last Reviewed: September 18, 2008</b>

**\*\*Note: Community Health Plan uses these guidelines only for Rheumatoid Arthritis. For Non-Hodgkins Lymphoma and other conditions, CHP uses the Milliman Care Guidelines® criteria.**

## 1. Background:

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody specifically directed against CD20, a transmembrane protein found on the surface of B-cells.<sup>1</sup> CD20 is expressed on >90% of B-cell non-Hodgkin's lymphomas (NHL)<sup>2</sup> but is not found on hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues.<sup>3</sup> CD20 regulates early steps in the activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion channel.<sup>4</sup> B-cells are also now believed to play a role in the pathogenesis of rheumatoid arthritis at multiple sites in the autoinflammatory process including production of rheumatoid factor and other autoantibodies, antigen presentation, T-cell activation, and proinflammatory cytokine production.

Rituximab received FDA approval in November 1997 for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma (NHL). In April 2001, a supplemental Biologics License Application was approved for Rituxan for these additional uses: retreatment of patients with rituximab who have relapsed following initial rituximab therapy, use of eight weekly doses (compared to original four) per course of treatment, and treatment of patients with bulky disease (lesions > 10 cm). In February 2006, the FDA approved rituximab for the first-line treatment of diffuse large B-cell, CD20-positive, non-Hodgkin's lymphoma (DLBCL- a type of NHL) in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or other anthracycline-based chemotherapy regimens. Also in February 2006, the FDA approved rituximab in combination with methotrexate for the treatment of moderately- to severely-active rheumatoid arthritis in patients who have had an inadequate response to one or more TNF antagonist therapies.<sup>5</sup>

Rituximab is administered parenterally. Therefore, it is not generally covered under retail pharmacy benefits. Availability of published evidence for its use in patients with RA is currently limited<sup>6, 7, 8</sup> and long-term efficacy and safety remains a concern.

The Randomized Evaluation of Long-term Efficacy of Rituximab in RA (REFLEX) study was a randomized, double-blind, multicenter, placebo-controlled, phase 3 trial that included 520 patients with active RA refractory to one or more anti-TNFs + MTX. Patients were randomized to treatment with rituximab 1000 mg or placebo IV given on days 1 & 15, MTX 10-25

mg/week, 100 mg IV methylprednisolone immediately prior to each infusion, and oral glucocorticoid therapy between the two rituximab infusions. The primary efficacy endpoint was the proportion of patients achieving an ACR20 response at 24 weeks.

**Table 1: 24-Week Results from the Phase III REFLEX Trial**

Endpoint	Rituximab 2 x 1000 mg (n=298)	Placebo (n=201)	P-value
ACR20	51%	18%	<.0001
ACR50	27%	5%	<.0001
ACR70	12%	1%	<.0001

**\*\*FDA Warning (Posted 12/18/2006):**

FDA and Genentech informed healthcare professionals of important emerging safety information about Rituxan. Two patients died after being treated with Rituxan for systemic lupus erythematosus (SLE). Rituxan is approved for non-Hodgkin's lymphomas and rheumatoid arthritis and is prescribed off-label for other serious diseases and conditions such as SLE. The cause of death was a viral infection of the brain called progressive multifocal leukoencephalopathy (PML) that is caused by reactivated JC virus which is present in about 80 percent of adults. Physicians should maintain a high index of suspicion for the development of PML in patients under treatment with Rituxan.

**2. Indications/Criteria:**

**Rheumatoid Arthritis**

The use of rituximab may be considered medically necessary for rheumatoid arthritis in patients (age • 18 years) meeting all of the following criteria:

- Diagnosis of moderate to severe RA (Class II-IV) as defined by American College of Rheumatology.
- Previous trial and failure with one formulary TNF-alpha inhibitor (TNFI) (etanercept [Enbrel®] or adalimumab [Humira™]), unless contraindications to use of a TNFI are present.
- Patient's therapeutic plan includes concurrent therapy with methotrexate.
- Patient's therapeutic plan does not include concurrent therapy with a TNFI (e.g., adalimumab [Humira™], etanercept [Enbrel®] or infliximab [Remicade®]), anakinra (Kineret™) or abatacept (Orencia®).
- Dosing should not exceed 1 treatment course (two infusions with infusions separated by two weeks) every 6 months.

Retreatment Criteria:

- Retreatment with rituximab (Rituxan™) may be approved at a maximum of 2 courses in a 12 month time period based on the following criteria:
  - \* An improvement in any 1 of the following American College of Rheumatology assessment components for improvement:
    - painful joint count
    - swollen joint count
    - patient pain assessment
    - patient global assessment
    - physician global assessment
    - patient self-assessed disability
    - acute phase reactants (ESR or CRP)

**3. Limitations/Exclusions:**

<b>Healthy Options:</b>	None; pre-authorization required.
<b>Basic Health Plan:</b>	None; pre-authorization required.
<b>GAU:</b>	None; pre-authorization required.
<b>Medicare Advantage:</b>	None; pre-authorization required.

**4. Required Review and Approvals:**

Rituximab (Rituxan®) infusions require prior authorization by the CHP Medical Director or his/her designee. Each authorization period will be for six months.

**5. References:**

<sup>1</sup>Genentech, Inc. Rituxan® (rituximab) prescribing information. South San Francisco (CA): Genentech, Inc; 2006 Feb.

<sup>1</sup> Anderson KC, Bates MP, Slaughenhaupt BL, et al. Expression of human B cell-associated antigens on leukemias and lymphomas: A model of human B cell differentiation. *Blood* 1984;63(6):1424-1433.

<sup>1</sup> Tedder TF, Boyd AW, Freedman AS, et al. The B cell surface molecule B1 is functionally linked with B-cell activation and differentiation. *J Immunol* 1985;135(2):973-9.

<sup>1</sup> Tedder TF, Zhou LJ, Bell PD, et al. The CD20 surface molecule of B lymphocytes functions as a calcium channel. *J Cell Biochem* 1990;14D:195.

<sup>1</sup> US Food and Drug Administration Center for Drug Evaluation and Research. Rituximab Approval History. [Online]. [cited 2006 May 17]. Available from URL: [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label\\_ApprovalHistory#apphist](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist).

<sup>1</sup> Cohen SB, Greenwald M, Dougados MR, et al. Efficacy and safety of rituximab in active RA patients who experienced an inadequate response to one or more anti-TNF a therapies (REFLEX study). Presented at: The Annual Scientific Meeting of the American College of Rheumatology: Abstract #1830; 2005 Nov 12-17. San Diego (CA).

<sup>1</sup> Emery P, Filipowicz-Sosnowska A, Szczepanski L, et al. Primary analysis of a double-blind, placebo-controlled, dose-ranging trial of rituximab, an anti-CD20 monoclonal antibody, in patients with rheumatoid arthritis receiving methotrexate (DANCER trial). Presented at: The European League Against Rheumatism Meeting: Abstract #OP0008; 2005. Vienna (Austria).

<sup>1</sup> Emery P, Fleischmann RM, Filipowicz-Sosnowska A, et al. Rituximab in rheumatoid arthritis: a double-blind, placebo-controlled, dose-ranging trial. Presented at: The 2005 ACR/ARHP Annual Scientific Meeting: Abstract #1917; 2005 Nov 12-17. San Diego (CA).

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<sup>3</sup> Tedder TF, Boyd AW, Freedman AS, et al. The B cell surface molecule B1 is functionally linked with B-cell activation and differentiation. *J Immunol* 1985;135(2):973-9.

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<sup>5</sup> US Food and Drug Administration Center for Drug Evaluation and Research. Rituximab Approval History. [Online]. [cited 2006 May 17]. Available from URL:

[http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label\\_ApprovalHistory#apphist](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist).

<sup>6</sup> Cohen SB, Greenwald M, Dougados MR, et al. Efficacy and safety of rituximab in active RA patients who experienced an inadequate response to one or more anti-TNF a therapies (REFLEX study). Presented at: The Annual Scientific Meeting of the American College of Rheumatology: Abstract #1830; 2005 Nov 12-17. San Diego (CA).

<sup>7</sup> Emery P, Filipowicz-Sosnowska A, Szczepanski L, et al. Primary analysis of a double-blind, placebo-controlled, dose-ranging trial of rituximab, an anti-CD20 monoclonal antibody, in patients with rheumatoid arthritis receiving methotrexate (DANCER trial). Presented at: The European League Against Rheumatism Meeting: Abstract #OP0008; 2005. Vienna (Austria).

<sup>8</sup> Emery P, Fleischmann RM, Filipowicz-Sosnowska A, et al. Rituximab in rheumatoid arthritis: a double-blind, placebo-controlled, dose-ranging trial. Presented at: The 2005 ACR/ARHP Annual Scientific Meeting: Abstract #1917; 2005 Nov 12-17. San Diego (CA).