BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Rituximab (Rituxan®)

Policy # 00218
Original Effective Date: 10/18/2006
Current Effective Date: 06/18/2014

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of rituximab (Rituxan®)‡ to be **eligible for coverage** for any of the following conditions:

- For treatment of non-Hodgkin's lymphoma (NHL);
- For treatment of mantel cell lymphoma;
- For treatment of chronic lymphocytic leukemia;
- For treatment of relapsed/ refractory Waldenstrom's macroglobulinemia;
- For treatment of immune or idiopathic thrombocytopenic purpura;
- For use in combination with corticosteroids for the treatment of adults with Wegener's Granulomatosis (WG) or Microscopic Polyangiitis (MPA).

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of rituximab (Rituxan) for the treatment of moderate to severe rheumatoid arthritis to be **eligible for coverage** when patient selection criteria are met.

Patient Selection Criteria
Coverage eligibility for the use of rituximab (Rituxan) for the treatment of rheumatoid arthritis will be considered when all of the following criteria are met:

- Patient is 18 years or older; and
- Failed treatment with one or more tumor necrosis factor (TNF) antagonist therapies (e.g. Enbrel®)‡; and
- Rituxan is used in combination with methotrexate.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

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Based on review of available data, the Company considers the use of rituximab (Rituxan) when patient selection criteria are not met to be **investigational.***

Based on review of available data, the Company considers the use of rituximab (Rituxan) for non-FDA approved indications, including but not limited to the following, to be **investigational*:**

- For treatment of conditions not listed as eligible for coverage; or
- When patient selection criteria for rheumatoid arthritis are not met; or
- Systemic Lupus Erythematosus (SLE).

Background/Overview

A monoclonal antibody is a laboratory-produced substance that can locate and bind to cancer cells wherever they are in the body. Many monoclonal antibodies are used in cancer detection or therapy; each one recognizes a different protein on certain cancer cells. Monoclonal antibodies can be used alone, or they can be used to deliver drugs, toxins, or radioactive material directly to a tumor.

Rituxan is considered a first-line treatment of patients with diffuse large B-cell, CD20-positive, NHL in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or other anthracycline-based chemotherapy regimens. It depletes B-cells that have CD20 on their surface (including pre-B cells through mature B-cells; but not stem cells or plasma cells) by several effector mechanisms.

Lymphoma

Lymphoma is a cancer that begins in cells of the immune system. There are two basic categories of lymphomas. One kind is Hodgkin's lymphoma, which is marked by the presence of a type of cell called the Reed-Sternberg cell. The other category is NHL, which includes a large, diverse group of cancers of immune system cells. NHL can be further divided into cancers that have an indolent (slow-growing) course and those that have an aggressive (fast-growing) course. These subtypes behave and respond to treatment differently. Both Hodgkin's and NHL can occur in children and adults, and prognosis and treatment depend on the stage and the type of cancer.

Chronic lymphocytic leukemia is a cancer of the white blood cells which causes a slow increase in the number of B lymphocytes in the bone marrow. The cancerous cells spread from the blood marrow to the blood and can affect the lymph nodes and other organs.

Waldenstrom’s macroglobulinemia is a cancer of the B lymphocytes and is associated with the overproduction of IgM antibodies.

Non-Hodgkin's Lymphoma (NHL)

There are many types of NHL. Non-Hodgkin's lymphoma begins when a lymphocyte (a B-cell or T-cell) becomes abnormal and usually starts in a B-cell in a lymph node. Although NHL can occur in young people, the chance of developing this disease goes up with age. Most people with non-Hodgkin's lymphoma are older than 60.

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Rheumatoid Arthritis (RA)
Rheumatoid arthritis is an autoimmune disease that causes inflammation of the joints and surrounding tissues. It can also affect other organs. Rheumatoid arthritis usually occurs in people between 25 and 55. This condition usually requires lifelong treatment, including medications, physical therapy, exercise, education and possibly surgery.

Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA) are forms of vasculitis (inflammation of blood vessels) that affects the nose, lungs, kidneys, and other organs. Due to its end-organ damage, it is life-threatening and requires long-term immunosuppression.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
In 1997 the FDA approved Rituxan for the treatment of relapsed or refractory, low-grade or follicular, CD20 positive, B-cell NHL. In 2006, the FDA granted Rituxan a supplemental approval for the treatment of diffuse large B-cell NHL in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or other anthracycline-based chemotherapy regimens in previously untreated patients.

In 2006 Rituxan was approved to be marketed specifically for the treatment of refractory RA.

On 1/28/2011, the FDA approved a new expanded indication for rituximab for previously untreated follicular CD20-positive, B-cell NHL in combination with first-line chemotherapy and, in patients achieving a complete (CR) or partial response (PR) to Rituxan in combination with chemotherapy, as single-agent maintenance therapy.

In 2011, the prescribing information for Genentech/Biogen Idec's Rituxan (rituximab) was expanded to include a new indication for use in combination with corticosteroids for the treatment of adults with WG and MPA.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Rituximab binds to the antigen CD20 found on normal and malignant B lymphocytes. Administration of rituximab results in a rapid and sustained depletion of circulating and tissue-based B-Cells. Lymph node biopsies performed 14 days after therapy showed a decrease in the percentage of B-cells in 7 of 8 patients with NHL who had received single doses of rituximab.

2002 TEC criteria assessment approved the use of rituximab for patients with low-grade B-cell NHL who had not responded to standard treatments. It is designed to target and destroy white blood cells involved in the disease, resulting in significant tumor shrinkage. Because rituximab targets specific cells rather than all

fast-growing cells there are fewer side effects than most chemotherapy. Patients are at an increased risk of developing infections since rituximab destroys healthy immune cells.

In NHL studies, administration of rituximab resulted in a rapid and sustained depletion of circulating and tissue-based B cells. Lymph node biopsies performed 14 days after therapy showed a decrease in the percentage of B-cells in 7 of 8 patients with NHL who had received single doses of rituximab. Circulating B-cells were depleted within the first 3 doses with sustained depletion for up to 6 to 9 months post-treatment in 83% of patients. B-cell recovery began at approximately six months following completion of treatment. Median B-cell levels returned to normal by 12 months following completion of treatment.

B-cells are believed to play a role in the pathogenesis of 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 auto antibodies, antigen presentation, T-cell activation and/or pro-inflammatory cytokine production.

In RA studies, treatment with rituximab induced depletion of peripheral B Lymphocytes, with all patients demonstrating near complete depletion within two weeks after receiving the first dose of rituximab. The majority of patients showed peripheral B-cell depletion for at least six months. A small portion of patients had prolonged peripheral B-cell depletion lasting more than three years after a single course of treatment.

The pharmacokinetics of rituximab have not been studied in children and adolescents. No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of rituximab. United States Pharmacopoeia Dispensing Information (USPDI) accepted usages include: lymphoma, relapsed/refractory chronic lymphocytic leukemia, Waldenstrom's macroglobulinemia and immune or idiopathic thrombocytopenic purpura.

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2013 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J9310
ICD-9 Diagnosis	200.40 thru 200.48, 202.01 thru 202.28, 204.00 thru 204.92
ICD-9 Procedure	No codes

Policy History

Original Effective Date: 10/18/2006
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10/04/2006	Medical Director Review
10/18/2006	Medical Policy Committee approval
12/05/2007	Medical Director review
12/19/2007	Medical Policy Committee approval. Coverage eligibility changed for treatment of Waldenstrom's Macroglobulinemia and Idiopathic Thrombocytopenia Purpura.
12/03/2008	Medical Director review
12/17/2008	Medical Policy Committee approval. No change to coverage eligibility.
12/04/2009	Medical Policy Committee approval
12/16/2009	Medical Policy Implementation Committee approval. Added that when patient selection criteria are not met, or if infliximab is used for non-FDA approved indications, to deny investigational.
12/01/2010	Medical Policy Committee review
12/15/2010	Medical Policy Implementation Committee approval. Format revision; including, addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
06/02/2011	Medical Policy Committee review
06/15/2011	Medical Policy Implementation Committee approval. Added coverage for use in combination with corticosteroids for the treatment of adults with Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)
06/14/2012	Medical Policy Committee review
06/20/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/06/2013	Medical Policy Committee review
06/25/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/05/2014	Medical Policy Committee review

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06/18/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 06/2015

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. in accordance with nationally accepted standards of medical practice;
B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.