



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Effective Date..... 7/15/2011
Next Review Date.....7/15/2012
Coverage Policy Number..... 5108

Subject **Rituximab (Rituxan®)**

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Coverage Policy

CIGNA covers rituximab (Rituxan®) as medically necessary for any of the following indications when the associated criteria are met:

- active rheumatoid arthritis (RA) in an adult when used in combination with methotrexate when **EITHER** of the following criteria is met:
 - history of a beneficial clinical response to rituximab (Rituxan®)
 - inadequate response, intolerance, or contraindication to at least one disease-modifying anti-rheumatic drugs (DMARDs) (i.e., Methotrexate (MTX) Azathioprine, gold, Hydroxychloroquine, leflunomide, Penicillamine, Leflunomide, Sulfasalazine) **AND to ONE self administered preferred** tumor necrosis factor (TNF) antagonist [adalimumab (Humira®) or etanercept (Enbrel®)]
- chronic lymphocytic leukemia (CLL)
- Hodgkin lymphoma
- immune or idiopathic thrombocytopenic purpura
- multicentric Castleman disease
- non-Hodgkin lymphoma (NHL)
- primary central nervous system lymphoma
- Waldenstrom macroglobulinemia

- Wegener granulomatosis (WG)
- Microscopic polyangiitis (MPA)

CIGNA does not cover the use of rituximab (Rituxan®) for any other indication because it is considered experimental, investigational or unproven.

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to rituximab (Rituxan®) therapy.

FDA Approved Indications

Non-Hodgkin's Lymphoma (NHL)

Rituxan is indicated for the treatment of patients with:

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to Rituxan in combination with chemotherapy, as single-agent maintenance therapy.
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens

Chronic Lymphocytic Leukemia (CLL)

Rituxan is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL.

Rheumatoid Arthritis (RA)

Rituxan in combination with methotrexate is indicated for the treatment of adult patients with moderately- to severely- active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

Rituxan, in combination with glucocorticoids, is indicated for the treatment of adult patients with Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA).

FDA Recommended Dosing

Initiate infusion at a rate of 50 mg/hr. In the absence of infusion toxicity, increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. For subsequent infusion, initiate infusion at a rate of 100 mg/hr. In the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.

NHL

The recommended dose is 375 mg/m² as an intravenous infusion according to the following schedules:

- **Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL** - Administer once weekly for 4 or 8 doses.
- **Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL** - Administer once weekly for 4 doses.
- **Previously Untreated, Follicular, CD20-Positive, B-Cell NHL** - Administer on Day 1 of each cycle of chemotherapy, for up to 8 doses. In patients with complete or partial response, initiate Rituxan maintenance eight weeks following completion of Rituxan in combination with chemotherapy. Administer Rituxan as a single-agent every 8 weeks for 12 doses.
- **Non-progressing, Low-Grade, CD20-Positive, B-cell NHL, after first-line CVP chemotherapy** - Following completion of 6–8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses.

- **Diffuse Large B-Cell NHL** - Administer on Day 1 of each cycle of chemotherapy for up to 8 infusions.

CLL

The recommended dose is 375 mg/m² the day prior to the initiation of FC chemotherapy, then 500 mg/m² on Day 1 of cycles 2–6 (every 28 days).

RA

Administer Rituxan as two-1000 mg intravenous infusions separated by 2 weeks. Glucocorticoids administered as methylprednisolone 100 mg intravenous or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion reactions. Subsequent courses should be administered every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks. Rituxan is given in combination with methotrexate.

WG and MPA

Administer Rituxan as a 375 mg/m² intravenous infusion once weekly for 4 weeks. Glucocorticoids administered as methylprednisolone 1000 mg intravenously per day for 1 to 3 days followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day and tapered per clinical need) are recommended to treat severe vasculitis symptoms. This regimen should begin within 14 days prior to or with the initiation of Rituxan and may continue during and after the 4 week course of Rituximab treatment. Safety and efficacy of treatment with subsequent courses of Rituxan have not been established.

Black Box Warning

Infusion Reactions - Rituxan administration can result in serious, including fatal infusion reactions. Deaths within 24 hours of Rituxan infusion have occurred. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. Carefully monitor patients during infusions. Discontinue Rituxan infusion and provide medical treatment for Grade 3 or 4 infusion reactions. **Tumor Lysis Syndrome (TLS)** - Acute renal failure requiring dialysis with instances of fatal outcome can occur in the setting of TLS following treatment of Non-Hodgkin lymphoma (NHL) with Rituxan monotherapy. **Severe Mucocutaneous Reactions** - Severe, including fatal, mucocutaneous reactions can occur in patients receiving Rituxan. **Progressive Multifocal Leukoencephalopathy (PML)** - JC virus infection resulting in PML and death can occur in patients receiving Rituxan.

Drug Availability

Rituxan vials are available in 100 mg and 500 mg strengths and are stable at 2°C–8°C (36°F–46°F). Do not use beyond expiration date stamped on carton.

General Background

Pharmacology

Rituximab is a chimeric monoclonal antibody directed against transmembrane CD20 proteins on the surface of immature and mature B lymphocytes. The effect of rituximab binding to these proteins is cell lysis and a reduction in antibody-producing capacity. This results in a lowered autoimmune activity in RA. Infusions of rituximab in patients with RA have less variability than patients with lymphoma. It has a small volume of distribution of 4.3 L and a long circulating half-life of 19 days.

Guidelines

National Comprehensive Cancer Network (NCCN)

The NCCN recommends Rituxan for the following indications:

Primary Central Nervous System Lymphoma

Grade 2A

Intracerebrospinal fluid (CSF) treatment for leptomeningeal metastases following radiation therapy (RT) as primary treatment for good-risk patients with normal CSF flow; as maintenance therapy for patients with negative CSF cytology; for clinically stable or improving patients with positive CSF cytology without progression; or as second-line treatment in patients with positive CSF cytology and progression.

Primary treatment combined with high-dose methotrexate, vincristine, procarbazine, and cytarabine and with or without radiation therapy.

Treatment as a single agent or in combination with temozolomide for progressive disease in patients who have received prior methotrexate-based regimen without prior radiation therapy after prolonged response to prior regimen or in combination with radiation therapy after short or no response to prior regimen.

Consider systemic and/or intracerebrospinal fluid treatment as a single agent or in combination with temozolomide for progressive or recurrent disease in patients with prior whole brain radiation therapy.

Hodgkin Lymphoma

Grade 2A

Primary treatment with or without radiation therapy for patients with stage IB or IIB or stage III-IV disease as a single agent or as a component of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) regimen; CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen; CVP (cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone) regimen; EPOCH (cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone) regimen.

NHL - Diffuse large B-cell lymphoma

Grade 1

First-line therapy for stage I-II disease as a component of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) regimen with rituximab.

First-line therapy for stage III to IV disease as a component of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen with rituximab; dose-dense CHOP 14 regimen with rituximab; dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen with rituximab.

Grade 2A

First-line therapy in patients with poor left ventricular function as a component of CEPP (cyclophosphamide, etoposide, prednisone, and procarbazine) regimen with rituximab; CDOP (cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone) regimen with rituximab; CNOP (cyclophosphamide, mitoxantrone, vincristine, and prednisone) regimen with rituximab; dose-adjusted EPOCH regimen with rituximab; CEOP (cyclophosphamide, etoposide, vincristine, and prednisone) regimen with rituximab.

Second-line therapy for relapsed or refractory disease as a component of DHAP (dexamethasone, cisplatin, and cytarabine), ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin), GDP (gemcitabine, dexamethasone, and cisplatin), GemOX (gemcitabine and oxaliplatin), ICE (ifosfamide, carboplatin, and etoposide), or MINE (mesna, ifosfamide, mitoxantrone, and etoposide) regimen with rituximab in patients with intention to proceed to high-dose therapy with autologous stem cell rescue; as a single agent, in combination with lenalidomide, or as a component of CEPP (cyclophosphamide, etoposide, prednisone, and procarbazine), dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), CEOP (cyclophosphamide, etoposide, vincristine, and prednisone), GDP, or GemOX regimen with rituximab in noncandidates for high-dose therapy.

NHL - AIDS-Related B-Cell Lymphoma

Grade 2A

In combination with growth factor support for AIDS-related Burkitt lymphoma as a component of CODOX-M (cyclophosphamide, doxorubicin, and vincristine, with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) regimen alternating with IVAC (ifosfamide, cytarabine, etoposide, and intrathecal methotrexate) regimen with rituximab; dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen with rituximab for favorable presentation; CDE (cyclophosphamide, doxorubicin, and etoposide) regimen with rituximab for favorable presentation; CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen with high-dose methotrexate and with rituximab for favorable presentation.

In combination with growth factor support for CD20+ AIDS-related diffuse large B-cell lymphoma and lymphoma associated with Castleman's disease as a component of dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen with rituximab; CDE (cyclophosphamide, doxorubicin, and etoposide) regimen with rituximab; CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen with rituximab; CDOP (cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone) regimen with rituximab.

Second-line therapy for relapse of AIDS-related diffuse large B-cell lymphoma and lymphoma associated with Castleman's disease as a component of DHAP (dexamethasone, cisplatin, and cytarabine), ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin), GDP (gemcitabine, dexamethasone, and cisplatin), GemOX (gemcitabine and oxaliplatin), ICE (ifosfamide, carboplatin, and etoposide), or MINE (mesna, ifosfamide, mitoxantrone, and etoposide) regimen with rituximab in patients with intention to proceed to high-dose therapy with autologous stem cell rescue or as a single agent, in combination with lenalidomide, or as a component of CEPP (cyclophosphamide, etoposide, prednisone, and procarbazine), dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), CEOP (cyclophosphamide, etoposide, vincristine, and prednisone), GDP, or GemOX regimen with rituximab in noncandidates for high-dose therapy.

NHL - Burkitt Lymphoma

Grade 2A

Induction therapy for low-risk disease as a component of CODOX-M (cyclophosphamide, doxorubicin, and vincristine, with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) regimen (original or modified) with rituximab; dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen with rituximab and intrathecal methotrexate; HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine regimen with rituximab.

Induction therapy for high-risk disease as a component of CODOX-M (cyclophosphamide, doxorubicin, and vincristine, with intrathecal methotrexate and cytarabine followed by high-dose systemic methotrexate) regimen (original or modified) alternating with IVAC (ifosfamide, cytarabine, etoposide, and intrathecal methotrexate) regimen with rituximab; dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen with rituximab and intrathecal methotrexate for patients not able to tolerate aggressive therapy; HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine regimen with rituximab.

Second-line therapy for relapse of Burkitt lymphoma following complete response as a component of dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen with rituximab and intrathecal methotrexate; RIVAC (rituximab, ifosfamide, cytarabine, etoposide, and intrathecal methotrexate) if not previously given; RGDP (rituximab, gemcitabine, dexamethasone, and cisplatin) regimen.

NHL – CLL

Grade 2A

First-line therapy for stage II-IV disease as single-agent therapy in patients unable to tolerate purine analogs or for CLL without del(17p) or with or without del(11q) in patients age 70 years or older or in younger patients with comorbidities; in combination with alemtuzumab, bendamustine, or high-dose methylprednisolone for CLL with del(17p); in combination with bendamustine for CLL without del(17p) or with or without del(11q); in combination with cyclophosphamide and prednisone for CLL without del(17p) or with or without del(11q) in patients age 70 years or older or younger patients with comorbidities; in combination with fludarabine for CLL without del(11q) or with or without del(17p); as a component of PCR (pentostatin, cyclophosphamide, and rituximab) regimen for CLL without del(17p) or with or without del(11q) in patients less than age 70 years or in older patients without significant comorbidities; as a component of FCR (fludarabine, cyclophosphamide, and rituximab) regimen for CLL without del(17p) or with or without del(11q) in patients less than age 70 years or in older patients without significant comorbidities or for CLL with del(17p); as a component of reduced-dose FCR for CLL with del(11q) in patients age 70 years or older or in younger patients with comorbidities.

Therapy for relapsed or refractory CLL without del(11q) or del(17p) as a single agent, in combination with bendamustine, or as a component of cyclophosphamide and prednisone with rituximab, FCR (fludarabine, cyclophosphamide, and rituximab), FR (fludarabine and rituximab) or PCR (pentostatin, cyclophosphamide, and rituximab) regimen for patients with a long response (more than 3 years) to first-line therapy; with del(11q) as a

single agent, in combination with bendamustine, or as a component of cyclophosphamide and prednisone with rituximab, FCR, reduced-dose FCR, or PCR regimen; without del(17p) or with or without del(11q) as a single agent in a dose-dense regimen, in combination with alemtuzumab, bendamustine or high-dose methylprednisolone, or in reduced-dose FCR or PCR regimen in patients age 70 years or older or in younger patients with comorbidities who have a short response (less than 2 years) to first-line therapy; without del(17p) or with or without del(11q) in combination with bendamustine, alemtuzumab, or high-dose methylprednisolone or as a component of FCR, PCR, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with rituximab, HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine with rituximab, dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) with rituximab, or OFAR (oxaliplatin, fludarabine, cytarabine, and rituximab) regimen in patients less than age 70 years or in older patients without significant comorbidities with a short response (less than 2 years) to first-line therapy.

Therapy for relapsed or refractory CLL with del(17p) in combination with alemtuzumab, bendamustine, or high-dose dexamethasone or as a component of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with rituximab regimen; HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine with rituximab regimen; OFAR (oxaliplatin, fludarabine, cytarabine, and rituximab) regimen; CFAR (cyclophosphamide, fludarabine, alemtuzumab, and rituximab) regimen.

NHL - Follicular lymphoma and Nodal marginal zone lymphoma

Grade 1

First-line therapy as a single agent or in CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen with rituximab; CVP (cyclophosphamide, vincristine, and prednisone) regimen with rituximab; fludarabine with rituximab; FND (fludarabine, mitoxantrone, and dexamethasone) regimen with rituximab; bendamustine with rituximab; CHOP regimen with rituximab followed by radioimmunotherapy; CVP regimen with rituximab followed by radioimmunotherapy; fludarabine with rituximab followed by radioimmunotherapy; FND regimen with rituximab followed by radioimmunotherapy.

Second-line therapy for refractory or progressive disease in patients with the indications for treatment as a single agent or in bendamustine with rituximab; CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen with rituximab; CVP (cyclophosphamide, vincristine, and prednisone) regimen with rituximab; fludarabine with rituximab; FND (fludarabine, mitoxantrone, and dexamethasone) regimen with rituximab; FCMR (fludarabine, cyclophosphamide, mitoxantrone, and rituximab) regimen; DHAP (dexamethasone, cisplatin, and cytarabine) regimen with rituximab; ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin) regimen with rituximab; GDP (gemcitabine, dexamethasone, and cisplatin) regimen with rituximab; GemOX (gemcitabine and oxaliplatin) regimen with rituximab; ICE (ifosfamide, carboplatin, and etoposide) regimen with rituximab; MINE (mesna, ifosfamide, mitoxantrone, and etoposide) regimen with rituximab; CEPP (cyclophosphamide, etoposide, prednisone, and procarbazine) regimen with rituximab; dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen with rituximab; CEOP (cyclophosphamide, etoposide, vincristine, and prednisone) regimen with rituximab lenalidomide with rituximab

Maintenance therapy as first-line (up to two years) or second-line extended dosing.

Grade 2A

First-line therapy as a single agent or in combination with chlorambucil or cyclophosphamide in elderly or infirm patients with the indications for treatment in the setting of comorbidities where tolerability of combination chemotherapy is a concern.

NHL - Gastric MALT lymphoma

Grade 1

First-line therapy for stage III_E-IV disease as a single agent or in CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen with rituximab; CVP (cyclophosphamide, vincristine, and prednisone) regimen with rituximab; fludarabine with rituximab; FND (fludarabine, mitoxantrone, and dexamethasone) regimen with rituximab; bendamustine with rituximab; CHOP regimen with rituximab followed by radioimmunotherapy; CVP regimen with rituximab followed by radioimmunotherapy; fludarabine with rituximab followed by radioimmunotherapy; FND regimen with rituximab followed by radioimmunotherapy.

Second-line therapy for recurrent or progressive disease in patients with the indications for treatment as a single agent or in bendamustine with rituximab; CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen with rituximab; CVP (cyclophosphamide, vincristine, and prednisone) regimen with rituximab; fludarabine with rituximab; FND (fludarabine, mitoxantrone, and dexamethasone) regimen with rituximab; FCMR (fludarabine, cyclophosphamide, mitoxantrone, and rituximab) regimen; DHAP (dexamethasone, cisplatin, and cytarabine) regimen with rituximab; ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin) regimen with rituximab; GDP (gemcitabine, dexamethasone, and cisplatin) regimen with rituximab; GemOX (gemcitabine and oxaliplatin) regimen with rituximab; ICE (ifosfamide, carboplatin, and etoposide) regimen with rituximab; MINE (mesna, ifosfamide, mitoxantrone, and etoposide) regimen with rituximab; CEPP (cyclophosphamide, etoposide, prednisone, and procarbazine) regimen with rituximab; dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen with rituximab; CEOP (cyclophosphamide, etoposide, vincristine, and prednisone) regimen with rituximab; lenalidomide with rituximab.

Maintenance therapy as first-line (up to two years) or second-line extended dosing.

Grade 2A

Initial therapy as a single agent for patients with H. pylori-negative stage I_E-II_E disease if radiation is contraindicated.

First-line therapy as a single agent or in combination with chlorambucil or cyclophosphamide for stage III_E-IV disease in elderly or infirm patients with the indications for treatment in the setting of comorbidities where tolerability of combination chemotherapy is a concern.

NHL – Lymphoblastic Lymphoma

Grade 2A

Induction or reinduction therapy for stage I-IV disease as a component of HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) regimen with rituximab in CD20-positive disease and with imatinib in Philadelphia chromosome-positive disease.

NHL – Mantle Cell Lymphoma

Grade 2A

Induction therapy as a component of aggressive therapy with HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine regimen with rituximab; NORDIC (dose-intensified induction immunochemotherapy with rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone [maxi-CHOP] alternating with rituximab and high-dose cytarabine) regimen; rituximab + methotrexate with augmented CHOP (CALGB regimen); sequential RCHOP/RICE (rituximab, ifosfamide, carboplatin, and etoposide); sequential RCHOP/RDHAP (rituximab, dexamethasone, cisplatin, and cytarabine) regimen followed by cytarabine.

Induction therapy as a component of less aggressive therapy with bendamustine or cladribine; CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen with rituximab; CVP (cyclophosphamide, vincristine, and prednisone) with rituximab; dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen with rituximab; modified HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen with rituximab followed by rituximab maintenance in patients older than 65 years.

Second-line therapy for relapsed, refractory, or progressive disease in combination with bendamustine, bortezomib, cladribine, or lenalidomide or as a component of FC (fludarabine and cyclophosphamide) regimen with rituximab; PEPC (prednisone, etoposide, procarbazine, and cyclophosphamide) regimen with rituximab; PCR (pentostatin, cyclophosphamide, and rituximab) regimen; FMR (fludarabine, mitoxantrone, and rituximab) regimen; FCMR (fludarabine, cyclophosphamide, mitoxantrone, and rituximab) regimen; DHAP (dexamethasone, cisplatin, and cytarabine) regimen with rituximab; ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin) regimen with rituximab; GDP (gemcitabine, dexamethasone, and cisplatin) regimen (with rituximab); GemOX (gemcitabine and oxaliplatin) regimen with rituximab; ICE (ifosfamide, carboplatin, and etoposide) regimen with rituximab; MINE (mesna, ifosfamide, mitoxantrone and etoposide) regimen with rituximab; CEPP (cyclophosphamide, etoposide, prednisone, and procarbazine) regimen with rituximab; dose-

adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen with rituximab; CEOP (cyclophosphamide, etoposide, vincristine, and prednisone) regimen with rituximab.

NHL - Nongastric MALT lymphoma

Grade 1

First-line therapy for MALT lymphomas coexistent with large cell lymphoma as a component of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen with rituximab for stage I-II disease; CHOP with rituximab, dose-dense CHOP 14 with rituximab, or dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen with rituximab for stage III-IV disease.

First-line therapy for stage III-IV disease as a single agent or in CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen with rituximab; CVP (cyclophosphamide, vincristine, and prednisone) regimen with rituximab; fludarabine with rituximab; FND (fludarabine, mitoxantrone, and dexamethasone) regimen with rituximab; bendamustine with rituximab; CHOP regimen with rituximab followed by radioimmunotherapy; CVP regimen with rituximab followed by radioimmunotherapy; fludarabine with rituximab followed by radioimmunotherapy; FND regimen with rituximab followed by radioimmunotherapy.

Second-line therapy for recurrent stage I-II disease or for progressive disease in patients with the indications for treatment as a single agent or in bendamustine with rituximab; CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen with rituximab; CVP (cyclophosphamide, vincristine, and prednisone) regimen with rituximab; fludarabine with rituximab; FND (fludarabine, mitoxantrone, and dexamethasone) regimen with rituximab; FCMR (fludarabine, cyclophosphamide, mitoxantrone, and rituximab) regimen; DHAP (dexamethasone, cisplatin, and cytarabine) regimen with rituximab; ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin) regimen with rituximab; GDP (gemcitabine, dexamethasone, and cisplatin) regimen with rituximab; GemOX (gemcitabine and oxaliplatin) regimen with rituximab; ICE (ifosfamide, carboplatin, and etoposide) regimen with rituximab; MINE (mesna, ifosfamide, mitoxantrone, and etoposide) regimen with rituximab; CEPP (cyclophosphamide, etoposide, prednisone, and procarbazine) regimen with rituximab; dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen with rituximab; CEOP (cyclophosphamide, etoposide, vincristine, and prednisone) regimen with rituximab lenalidomide with rituximab.

Maintenance therapy as first-line (up to two years) or second-line extended dosing.

Grade 2A

First-line therapy as a single agent or in combination with chlorambucil or cyclophosphamide for stage III-IV disease in elderly or infirm patients with the indications for treatment in the setting of comorbidities where tolerability of combination chemotherapy is a concern.

First-line therapy for MALT lymphomas coexistent with large cell lymphoma in patients with poor left ventricular function as a component of CEPP (cyclophosphamide, etoposide, prednisone, and procarbazine) regimen with rituximab; CDOP (cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone) regimen with rituximab; CNOP (cyclophosphamide, mitoxantrone, vincristine, and prednisone) regimen with rituximab; dose-adjusted EPOCH regimen with rituximab; CEOP (cyclophosphamide, etoposide, vincristine, and prednisone) regimen with rituximab.

NHL - Posttransplant lymphoproliferative disorder (PTLD)

Grade 2A

Single-agent therapy as primary treatment for monomorphic or polymorphic PTLD; second-line treatment for persistent or progressive early lesions or for persistent or progressive monomorphic PTLD if reduction of immunosuppressive was used as initial therapy; maintenance therapy for polymorphic PTLD achieving complete response on primary treatment.

Used as a component of RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), RCHOEP (rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone), or RCVP (rituximab, cyclophosphamide, vincristine, and prednisone) regimen for patients who cannot tolerate anthracyclines as primary treatment of monomorphic or systemic polymorphic PTLD or second-line treatment of persistent or progressive monomorphic or polymorphic PTLD.

NHL - Primary Cutaneous B-cell Lymphoma

Grade 1

Therapy for primary cutaneous marginal zone or follicle center B-cell refractory generalized cutaneous disease or newly diagnosed or relapsed generalized extracutaneous disease as a single agent or in bendamustine with rituximab; CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen with rituximab; CVP (cyclophosphamide, vincristine, and prednisone) regimen with rituximab; fludarabine with rituximab; FND (fludarabine, mitoxantrone, and dexamethasone) regimen with rituximab; CHOP regimen with rituximab followed by radioimmunotherapy; CVP regimen with rituximab followed by radioimmunotherapy; fludarabine with rituximab followed by radioimmunotherapy; FND regimen with rituximab followed by radioimmunotherapy.

Second-line therapy for primary cutaneous marginal zone or follicle center B-cell refractory generalized cutaneous disease or relapsed generalized extracutaneous disease in patients with the indications for treatment as a single agent or in bendamustine with rituximab; CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen with rituximab; CVP (cyclophosphamide, vincristine, and prednisone) regimen with rituximab; fludarabine with rituximab; FND (fludarabine, mitoxantrone, and dexamethasone) regimen with rituximab; FCMR (fludarabine, cyclophosphamide, mitoxantrone, and rituximab) regimen; DHAP (dexamethasone, cisplatin, and cytarabine) regimen with rituximab; ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin) regimen with rituximab; GDP (gemcitabine, dexamethasone, and cisplatin) regimen with rituximab; GemOX (gemcitabine and oxaliplatin) regimen with rituximab; ICE (ifosfamide, carboplatin, and etoposide) regimen with rituximab; MINE (mesna, ifosfamide, mitoxantrone, and etoposide) regimen with rituximab; CEPP (cyclophosphamide, etoposide, prednisone, and procarbazine) regimen with rituximab; dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen with rituximab; CEOP (cyclophosphamide, etoposide, vincristine, and prednisone) regimen with rituximab lenalidomide with rituximab.

Grade 2A

Therapy for generalized T3 cutaneous primary cutaneous marginal zone or follicle center B-cell lymphoma as a single agent or as palliative chemotherapy in combination with CVP (cyclophosphamide, vincristine, and prednisone) regimen or chlorambucil.

Used as a single agent (preferred) or in combination with chlorambucil or cyclophosphamide for primary cutaneous marginal zone or follicle center B-cell generalized T3 cutaneous disease or newly diagnosed generalized extracutaneous disease in elderly or infirm patients with the indications for treatment in the setting of comorbidities where tolerability of combination chemotherapy is a concern.

First-line therapy for generalized cutaneous T3 primary cutaneous diffuse large B-cell lymphoma, leg type as a component of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) regimen with rituximab.

First-line therapy for solitary regional, T1-2 or extracutaneous primary cutaneous diffuse large B-cell lymphoma, leg type as a component of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) regimen with rituximab; dose-dense CHOP 14 regimen with rituximab; dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen with rituximab.

First-line therapy in patients with poor left ventricular function as a component of CEPP (cyclophosphamide, etoposide, prednisone, and procarbazine) regimen with rituximab; CDOP (cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone) regimen with rituximab; CNOP (cyclophosphamide, mitoxantrone, vincristine, and prednisone) regimen with rituximab; dose-adjusted EPOCH regimen with rituximab; CEOP (cyclophosphamide, etoposide, vincristine, and prednisone) regimen with rituximab.

Second-line therapy for relapsed or refractory primary cutaneous diffuse large B-cell lymphoma, leg type as a component of DHAP (dexamethasone, cisplatin, and cytarabine), ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin), GDP (gemcitabine, dexamethasone, and cisplatin), GemOX (gemcitabine and oxaliplatin), ICE (ifosfamide, carboplatin, and etoposide), or MINE (mesna, ifosfamide, mitoxantrone, and etoposide) regimen with rituximab in patients with intention to proceed to high-dose therapy with autologous stem cell rescue or as a single agent, in combination with lenalidomide, or as a component of CEPP (cyclophosphamide, etoposide, prednisone, and procarbazine), dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), CEOP (cyclophosphamide, etoposide, vincristine, and prednisone), GDP, or GemOX regimen with rituximab in noncandidates for high-dose therapy.

NHL - Splenic Marginal Zone Lymphoma

Grade 1

First-line therapy for progressive disease following initial treatment for splenomegaly as a single agent or in CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen with rituximab; CVP (cyclophosphamide, vincristine, and prednisone) regimen with rituximab; fludarabine with rituximab; FND (fludarabine, mitoxantrone, and dexamethasone) regimen with rituximab; bendamustine with rituximab; CHOP regimen with rituximab followed by radioimmunotherapy; CVP regimen with rituximab followed by radioimmunotherapy; fludarabine with rituximab followed by radioimmunotherapy; FND regimen with rituximab followed by radioimmunotherapy.

Second-line therapy for recurrent or progressive disease in patients with the indications for treatment as a single agent or in bendamustine with rituximab; CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen with rituximab; CVP (cyclophosphamide, vincristine, and prednisone) regimen with rituximab; fludarabine with rituximab; FND (fludarabine, mitoxantrone, and dexamethasone) regimen with rituximab; FCMR (fludarabine, cyclophosphamide, mitoxantrone, and rituximab) regimen; DHAP (dexamethasone, cisplatin, and cytarabine) regimen with rituximab; ESHAP (etoposide, methylprednisolone, cytarabine, and cisplatin) regimen with rituximab; GDP (gemcitabine, dexamethasone, and cisplatin) regimen with rituximab; GemOX (gemcitabine and oxaliplatin) regimen with rituximab; ICE (ifosfamide, carboplatin, and etoposide) regimen with rituximab; MINE (mesna, ifosfamide, mitoxantrone, and etoposide) regimen with rituximab; CEPP (cyclophosphamide, etoposide, prednisone, and procarbazine) regimen with rituximab; dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) regimen with rituximab; CEOP (cyclophosphamide, etoposide, vincristine, and prednisone) regimen with rituximab; lenalidomide with rituximab.

Maintenance therapy as first-line (up to two years) or second-line extended dosing.

Grade 2A

Single-agent therapy in symptomatic hepatitis C-negative patients with splenomegaly.

First-line therapy as a single agent or in combination with chlorambucil or cyclophosphamide in elderly or infirm patients upon disease progression following initial treatment for splenomegaly in the setting of comorbidities where tolerability of combination chemotherapy is a concern.

Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma

Grade 2A

Used as primary therapy, as salvage therapy for disease that does not respond to primary therapy, or for progressive or relapsed disease as a single agent; in combination with bortezomib with or without dexamethasone; in combination with thalidomide; in combination with cyclophosphamide and prednisone or dexamethasone; in combination with bendamustine (risk of stem cell toxicity and/or transformation unknown).

Used in combination with cladribine or fludarabine in nontransplant candidates as primary therapy or salvage therapy for disease that does not respond to primary therapy or for progressive or relapsed disease.

Consider for maintenance therapy in patients who achieve a complete or partial response to primary therapy.

American College of Rheumatology (ACR)

The ACR 2008 recommendations published in June 15, 2008 issue of Arthritis Care & Research include the use of nonbiologic and biologic therapies in patients with RA when starting or resuming these therapies. The 2008 ACR recommendations address five key areas including: the indications for use, monitoring for side-effects, assessing the clinical response, screening for tuberculosis which is a risk factor associated with biologic DMARDs, and the roles of cost and patient preference in choosing biologic agents under certain circumstances (i.e. high disease activity). The duration of RA disease duration, disease severity, and prognostic features were also considered when developing these recommendations. According to ACR guideline, it is important that RA patients be seen regularly to assess disease activity, evaluate disease severity, and determine whether alternative therapies are warranted. Because there was no evidence to support a specific recommendation on the frequency of provider visits, a specific and potentially arbitrary time frame is not recommended at this point. However, based on these recommendations, commonly used but not exclusive tools to assess the RA disease activity include: Disease Activity Score (DAS) in 28 joints, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Rheumatoid Arthritis Disease Activity Index, Patient Activity Scale (PAS), and

Routine Assessment Patient Index Data. In addition it is recommended to use the combinations of commonly used but not exclusive prognostic factors to evaluate the patients with RA, including: Health Assessment Questionnaire (HAQ) score, Evidence of radiographic erosions, Elevated erythrocyte sedimentation rate, Elevated C-reactive protein level, and elevated levels of rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) antibodies. Due to the absence of a single “gold standard” measure, multiple measures or pooled indices are used to determine a diagnosis, estimate prognosis, and to assess and monitor disease activity and response to treatment. Other commonly used measures in the clinical settings include: Visual Analogue scale (VAS), Likert scales of global response to pain by the patient/doctor, and Global Arthritis Score (GAS).

Although there are other non-biologic and biologic DMARDs that are either approved by the FDA or occasionally used for treating RA, only the non-biologic agents hydroxychloroquine, leflunomide, methotrexate, minocycline, and sulfasalazine and the biologics abatacept, adalimumab, etanercept, infliximab, and rituximab are included in the 2008 ACR recommendations. The following are the 2008 ACR recommendations for non-biologic and biologic DMARD use in RA:

- Initiating methotrexate or leflunomide therapy is recommended for most RA patients.
- Methotrexate plus hydroxychloroquine is endorsed for patients with moderate to high disease activity.
- The triple DMARD combination of methotrexate plus hydroxychloroquine plus sulfasalazine for patients with poor prognostic features and moderate to high levels of disease activity.
- Prescribing anti-TNF α agents including etanercept, infliximab, or adalimumab, along with methotrexate in early RA (less than 3 months) only for patients with high disease activity who had never received DMARDs. In intermediate- and longer-duration RA, anti-TNF α agents were recommended for patients who had failed to respond adequately to methotrexate therapy.
- Reserving abatacept and rituximab for patients with at least moderate disease activity and poor disease prognosis for whom methotrexate in combination with or sequential administration of other nonbiologic DMARDs led to an inadequate response.
- Avoiding the initiation or resumption of treatment with methotrexate, leflunomide, or biologic agents for patients with active bacterial infection, active herpes-zoster viral infection, active or latent tuberculosis, or acute or chronic hepatitis B or C.
- Not prescribing anti-TNF α agents to patients with a history of heart failure, with a history of lymphoma, or with multiple sclerosis or demyelinating disorders.
- Avoiding the initiation or resumption of methotrexate, leflunomide, or minocycline for RA patients planning for pregnancy and throughout the duration of pregnancy and breastfeeding.

Clinical Efficacy

Off-Label Covered Indications

Castleman Disease

Multicentric Castleman disease (MCD) is a rare lymphoproliferative disorder with systemic symptoms and poor prognosis and is characterized by an abnormal proliferation of polyclonal plasmablasts in the mantle zone of B-cell follicles. The disease is found primarily in chronic HIV carriers and is usually strictly associated with human herpes virus type 8 (HHV-8) coinfection, which is believed to play a key role in the pathogenesis of MCD. The disease is also diagnosed in HIV-negative patients, who are usually elderly or immunosuppressed; however, in about half of these cases, no evidence of HHV8 infection is found. The anti-CD20 monoclonal antibody rituximab is now the preferred treatment for HIV-positive MCD. However, it is not clear whether rituximab is effective in HIV-negative patients with MCD, particularly in the HHV8-positive subset.

A case of a 46 year old Zambian woman who presented with pyrexia, diarrhea and vomiting, confusion, lymphadenopathy, and renal failure. She rapidly developed multiple organ failure following the initiation of treatment of MCD with rituximab. Following admission to intensive care (ICU), she received prompt multi-organ support. After 21 days on the ICU she returned to the haematology medical ward, and was discharged in remission from her disease after 149 days in hospital. Rituximab, in conjunction with extensive organ support was effective treatment for MCD with associated multiple organ failure. There is, to our knowledge, only one other published report of its successful use in an ICU setting, where it was combined with cyclophosphamide, adriamycin and prednisolone. Reports such as ours support the notion that critically unwell patients with HIV and haematological disease can benefit from intensive care.

Two HIV-negative, HHV8-positive patients with MCD were treated with rituximab. In both cases, a significant clinical improvement was observed after the first two infusions, which was shortly followed by a drop in HHV8 viremia to undetectable levels. Both patients underwent complete clinical remission, which persisted without relapse at 30 and 9 months of follow-up, respectively. No reactivation of the Kaposi sarcoma found in a lymph node of one of the patients was observed. Our report, along with additional data present in the literature, suggests that rituximab may be an appropriate and safe first-line therapy for HIV-negative, HHV8-positive MCD.

Ongoing Studies

Rituxan is being studied for use in multiple sclerosis (MS) and neuromyelitis optica (NMO). At this time, however, there is insufficient published data in terms of safety and efficacy to support the use of Rituxan for these indications.

Multiple Sclerosis (MS)

In a phase II, double-blind, 48-week clinical trial involving 104 patients with relapsing–remitting multiple sclerosis, Hauser, et al. (2008) assigned 69 patients to receive 1000 mg of intravenous rituximab and 35 patients to receive placebo on days 1 and 15. The primary end point was the total count of gadolinium-enhancing lesions detected on magnetic resonance imaging scans of the brain at weeks 12, 16, 20, and 24. Clinical outcomes included safety, the proportion of patients who had relapses, and the annualized rate of relapse. As compared with patients who received placebo, patients who received rituximab had reduced counts of total gadolinium-enhancing lesions at weeks 12, 16, 20, and 24 ($p < 0.001$) and of total new gadolinium-enhancing lesions over the same period ($p < 0.001$); and these results were sustained for 48 weeks ($p < 0.001$). As compared with patients in the placebo group, the proportion of patients in the rituximab group with relapses was significantly reduced at week 24 (14.5% versus 34.3%, $p = 0.02$) and week 48 (20.3% versus 40.0%, $p = 0.04$). More patients in the rituximab group than in the placebo group had adverse events within 24 hours after the first infusion, most of which were mild-to-moderate events; after the second infusion, the numbers of events were similar in the two groups. The authors concluded that a single course of rituximab reduced inflammatory brain lesions and clinical relapses for 48 weeks. However, the authors noted that this phase II study was not designed to evaluate long-term safety or to detect uncommon adverse events. They stated that the safety and effectiveness of rituximab for the treatment of multiple sclerosis need to be validated by larger and longer-term controlled studies. MacFarland (2008) noted that a phase II clinical trial leaves many questions unanswered including the duration of the treatment effect, the effect of progression of disability, and most importantly the types of adverse events that may occur at low frequency. Issues of long-term safety of rituximab must still be addressed, given reports to the FDA of progressive multifocal leukoencephalopathy in patients with lupus who were treated with rituximab.

Neuromyelitis Optica (NMO)

Neuromyelitis optica (NMO) is an uncommon disease syndrome of the central nervous system (CNS) that affects the optic nerves and spinal cord. There is no cure for NMO, but there are therapies to treat an attack while it is happening, to reduce symptoms, and to prevent relapses. An initial attack of NMO is usually treated with a combination of a corticosteroid drug (methylprednisolone) to stop the attack, and an immunosuppressive drug (azathioprine) for prevention of subsequent attacks. If frequent relapses occur, some individuals may need to continue a low dose of steroids for longer periods. Plasma exchange (plasmapheresis) is a technique that separates antibodies out of the blood stream and is used with people who are unresponsive to corticosteroid therapy. Individuals with major disability will require the combined efforts of occupational therapists, physiotherapists, and social services professionals to address their complex rehabilitation needs.

There are two small studies that cite the use of rituximab for NMO and show promising outcomes. However, one follow up study in 2008 shows the results of a 2005 study failed to show positive results after a 2 year time frame. Further research including clinical trials need to be complete to establish rituximab's efficacy in the treatment of NMO.

Adverse Reactions

The most common adverse reactions reported with rituximab in patients with RA include hypertension, nausea, arthralgias, and upper respiratory tract infections. Potentially serious adverse effects include infusion reactions, serious infections and cardiovascular events. No drug interactions are expected with rituximab, although no formal interaction studies are known. Vaccine failure is a potential problem if they are administered following a dose of rituximab.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

HCPCS Codes	Description
J9310	Injection, Rituximab, 10 mg

ICD-9-CM Diagnosis Codes	Description
200.00-200.88	Non-Hodgkin lymphoma
200.50-200.58	Primary central nervous system lymphoma
201.00-201.98	Hodgkin disease
202.00-202.98	Non-Hodgkin lymphoma
204.10	Chronic lymphoid leukemia, without mention of having achieved remission, failed remission
204.12	Chronic lymphoid leukemia, in relapse
273.3	Macroglobulinemia
287.31	Immune thrombocytopenic purpura
446.0	Polyarteritis nodosa
446.4	Wegener's granulomatosis
714.0	Rheumatoid arthritis
714.1	Felty's syndrome
714.2	Other rheumatoid arthritis with visceral or systemic involvement
785.6	Enlargement of lymph nodes

Experimental/Investigational/Unproven and Not Covered:

ICD-9-CM Diagnosis Codes	Description
	All other codes

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	10/1/2008	5108	Rituximab (Rituxan®)
Great-West Healthcare	12/2006	P99.107.2	Rituxan

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