Medication Policy Manual

Policy No: dru214

Topic: rituximab containing products (Rituxan®, Rituxan Hycela™)

Date of Origin: May 12, 2010

Committee Approval Date: August 11, 2017

Next Review Date: August 2018

Effective Date: September 1, 2017

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Rituximab (Rituxan) is a monoclonal antibody that disables B-cells in the body’s immune system. It is used in the treatment of some types of cancers (e.g. non-Hodgkin’s lymphomas), as well as in some conditions where the immune system may become overactive. Rituximab is administered as an infusion: intravenous (IV) Rituxan or subcutaneous (SC) Rituxan Hycela.
Policy/Criteria

I. **For rituximab/hyaluronidase (Rituxan Hycela) for subcutaneous (SC) infusion:** Most contracts require prior authorization approval of rituximab/hyaluronidase SC (Rituxan Hycela) prior to coverage. Rituximab/hyaluronidase SC (Rituxan Hycela) may be considered medically necessary when at least one of criteria A through C below is met.

A. A diagnosis of **diffuse large B-cell lymphoma (DLBCL)**

OR

B. A diagnosis of **follicular lymphoma (FL)**

OR

C. A diagnosis of **chronic lymphocytic leukemia (CLL)**

II. **For rituximab (Rituxan) for intravenous (IV) infusion:** Most contracts require prior authorization approval of rituximab IV (Rituxan) prior to coverage.

A. **USE IN B-CELL MEDIATED CANCERS:**

   Rituximab IV (Rituxan) may be considered medically necessary when used in the treatment of B-cell mediated cancers including but not limited to those listed in Appendix 1.

B. **USE IN OTHER CONDITIONS:**

   Rituximab IV (Rituxan) may be considered medically necessary when at least one of criteria 1 through 16 below is met.

   1. A diagnosis of refractory **anti-NMDA receptor encephalitis** (a specific type of autoimmune encephalitis) when prior therapy with corticosteroids and IVIG has been ineffective, unless contraindicated or not tolerated

   OR

   2. A diagnosis of refractory **autoimmune hemolytic anemia (AIHA)** when an adequate course of corticosteroids (e.g. 1 mg/kg/day for a minimum of 3 weeks) is ineffective, unless contraindicated or not tolerated.

   OR

   3. A diagnosis of **Castleman’s disease** [unicentric (UCD) or multicentric (MCD)], (angiofollicular lymph node hyperplasia).

   OR

   4. Patients with refractory **immune (idiopathic) thrombocytopenic purpura (ITP)** when all of criteria a. through c. below are met.

   a. A diagnosis of chronic ITP is made by, or in consultation with a hematologist.

   AND

   b. Patient is at risk of spontaneous bleeding as demonstrated in chart notes by either one of the following criteria:
i. Platelet count is less than 20,000/mm$^3$.
OR
ii. Platelet count is less than 30,000/mm$^3$ accompanied by symptoms of bleeding.

AND
c. An adequate course of corticosteroids (e.g. prednisone 1 to 2 mg/kg for 2 to 4 weeks, or pulse dexamethasone 40 mg daily for 4 days) has been ineffective, unless contraindicated or not tolerated.

OR
5. A diagnosis of refractory Evans’s syndrome when at least two prior therapies have been ineffective, unless contraindicated or not tolerated.

OR
6. A diagnosis of refractory myasthenia gravis (MG) when plasmapheresis or IVIG are ineffective, unless contraindicated or not tolerated.

OR
7. A diagnosis of refractory myositis (such as dermatomyositis, polymyositis or autoimmune myositis), when all criteria a. through c. are met:
a. Documented muscle weakness and associated severe functional impairment
b. At least ONE of the following documented diagnostic criteria below:
   i. Evidence of myositis, demonstrated by abnormality of muscle biopsy, MRI, OR EMG.
   OR
   ii. Increased muscle enzymes levels (such as CPK, AST, LDH, and/or aldolase)
   OR
   iii. Cutaneous changes, including heliotrope dermatitis (rash on the upper eyelids) and Gottron’s papules (papules over the knuckles), not responding to oral corticosteroids, methotrexate, and/or another oral immunosuppressant
c. At least one other treatment has been ineffective or not tolerated (e.g., corticosteroids, azathioprine, methotrexate, or cyclophosphamide; see Appendix 4), unless all are contraindicated

OR
8. A diagnosis of CD20-positive B-cell post-transplant lymphoproliferative disorder (B-PTLD) when tapering of immunosuppressive medications is not effective or is contraindicated.
9. A diagnosis of **rheumatoid arthritis (RA)** when established by or in consultation with a rheumatologist (see Appendix 2) and criteria a. and b. below are met.
   a. There is clinical documentation that methotrexate was not effective after at least a 6 to 12 week treatment course based on one or more of the assessment components listed in Appendix 3, or that methotrexate was not tolerated or is contraindicated.

   **AND**
   
   b. Rituximab is given in combination with an oral DMARD (see Appendix 4) unless not tolerated or contraindicated.

**OR**

10. A diagnosis of **Waldenström’s macroglobulinemia**.

**OR**

11. A diagnosis of **Wegener's Granulomatosis or Microscopic Polyangiitis** [also known as antineutrophil cytoplasmic antibody-(ANCA) associated vasculitis] when prior therapy with cyclophosphamide plus corticosteroids has been ineffective, unless contraindicated or not tolerated.

**OR**

12. A diagnosis of **neuromyelitis optica (NMO)** when at least two prior therapies have been ineffective, unless contraindicated or not tolerated.

**OR**

13. A diagnosis of **refractory pemphigoid** (bullous pemphigoid, mucous membrane pemphigoid) or **refractory pemphigus** (pemphigus foliaceus, pemphigus vulgaris) when corticosteroids and at least one other immunosuppressive agents (such as azathioprine, mycophenolate mofetil, dapsone, or cyclophosphamide; See Appendix 4) have been ineffective, unless contraindicated or not tolerated.

**OR**

14. A diagnosis of **nephrotic syndrome** including **minimal change disease** and **focal segmental glomerulosclerosis** when corticosteroids and at least one other immunosuppressive agent (see Appendix 4) have been ineffective, unless contraindicated or not tolerated.

**OR**

15. Prevention or treatment of **antibody (Ab)-mediated transplant (solid organ) rejection** (also known as vascular rejection, humoral rejection) when either criteria a. or b. below are met.
   a. Prevention of antibody-mediated transplant rejection in patients who are listed to receive solid organ transplant and are highly sensitized [e.g. high panel-reactive antibodies (PRA)].

**OR**
b. Treatment of antibody-mediated rejection following solid organ transplant when the rejection is confirmed by biopsy or presence of panel-reactive antibodies (PRA).

**OR**

16. A diagnosis of **multiple sclerosis** when criteria a. and b. below are met

a. A definitive diagnosis of a multiple sclerosis that has been established by a specialist in neurology or multiple sclerosis.

**AND**

b. Criteria i or ii below is met

i. There is clinical documentation that at least one of the following disease modifying therapies for multiple sclerosis has been documented in clinical notes to be ineffective, contraindicated, or not tolerated:

<table>
<thead>
<tr>
<th>Drug Name</th>
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<tbody>
<tr>
<td>Dimethyl fumarate (Tecfidera)</td>
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<tr>
<td>Fingolimod (Gilenya)</td>
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<tr>
<td>Glatiramer acetate (Copaxone or Glatopa)</td>
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<tr>
<td>Interferon beta-1a (Avonex, Rebif)</td>
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<tr>
<td>Interferon beta-1b (Betaseron)</td>
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<tr>
<td>Natalizumab (Tysabri)</td>
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<td>Ocrelizumab (Ocrevus)</td>
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<tr>
<td>Peginterferon beta-1a (Plegridy)</td>
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</table>

**Ineffectiveness** is defined as meeting at least one of the following three criteria (A, B, or C) during treatment with one of these medications:

A. The patient continues to have clinical relapses (at least one clinical relapse in the past 12 months)
B. The patient continues to have CNS lesion progression as measured by MRI.
C. The patient continues to have worsening disability. Examples of worsening disability include, but are not limited to, decreased mobility, decreased ability to perform activities of daily living due to disease progression, or EDSS > 3.5.

**OR**

ii. The patient has had a particularly aggressive initial disease course, as defined by meeting at least one of the following:
A. An EDSS score of ≥4 within 5 years of onset
B. Multiple (two or more) relapses with incomplete resolution in the past year
C. At least two MRI studies showing new or enlarging T2 lesions or gadolinium-enhancing lesions despite treatment over 6 months.
D. The presence of spinal or brainstem lesions on MRI

III. Administration, Quantity Limitations, and Authorization Period
A. OmedaRx does not consider rituximab (IV or SC) to be a self-administered medication.
B. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

IV. Rituximab/hyaluronidase SC (Rituxan Hycela) is considered investigational when used for any other indication not specified in Section I above.

V. Rituximab IV (Rituxan) is considered investigational when used for all other conditions, including but not limited to:
A. Antiphospholipid antibody syndrome (APS)
B. Chronic graft versus host disease (GVHD)
C. Systemic lupus erythematosus (SLE)
D. Scleroderma [localized or systemic, (SSc)]
E. Sjögren’s syndrome

Position Statement

Summary

- Rituximab is a monoclonal antibody that binds to the CD20 antigen on B-lymphocytes which ultimately leads to cell death. Its primary use is in the treatment of B-cell mediated-cancers, such as non-Hodgkin’s lymphomas.

- Based on its ability to suppress the immune system, there is also great interest in using rituximab in the treatment of many different autoimmune diseases. The clinical benefit of rituximab in the majority of these conditions is evolving or not known.

- Rituximab may cause serious adverse effects (e.g. severe mucocutaneous reactions, reactivation of hepatitis B, and progressive multifocal leukoencephalopathy). It is important to consider the potential risk versus benefit prior to using it in a particular condition taking into account disease severity and availability of other treatment options.

- Rituximab is available for IV (Rituxan) infusion. Rituximab/hyaluronidase (Rituxan Hycela) is a subcutaneous (SC) formulation for injection under the skin with hyaluronidase. Hyaluronidase is used to facilitate a large volume SC injection and allows for a faster rate of rituximab dose administration (versus traditional IV infusion).
- Rituximab (Rituxan) for IV infusion has been available for many years with proven efficacy and safety in various different indications. However, rituximab/hyaluronidase (Rituxan Hycela) for SC infusion has only been studied in patients with follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and chronic lymphocytic leukemia (CLL).

**Clinical Efficacy**

**Rituximab/hyaluronidase (Rituxan Hycela) for SC infusion**

- Rituximab/hyaluronidase SC (Rituxan Hycela) was FDA-approved in 2017 based on non-inferiority to rituximab IV (Rituxan) in pharmacokinetic studies in patients with follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and chronic lymphocytic leukemia (CLL). The trials included secondary endpoints of overall response rate (ORR), a surrogate marker for clinical response. [1]

- However, at this time, there is no evidence to support the safety or efficacy of rituximab/hyaluronidase SC (Rituxan Hycela) in any other indications.

**B-cell Post-transplant Lymphoproliferative Disorder (PTLD)**

- Lymphoproliferative disorders can arise from chronic immunosuppression after solid organ transplant. These disorders are serious and potentially fatal. Most are large cell lymphomas, the majority of which are of the B-cell type. [2]

- The majority of lymphoproliferative disease lesions either resolve completely or significantly improve with a reduction in immunosuppression. [2]

- Rituximab has shown promise in patients with CD20-positive B-cell post-transplant lymphoproliferative disorder with overall response rates ranging from 44% to 68%. The evidence is of poor quality as it is based on case series (small populations, no control groups, and no blinding). [2,3]

**Chronic Immune (Idiopathic) Thrombocytopenic purpura (ITP)**

- Idiopathic thrombocytopenic purpura is an acquired disorder in which isolated thrombocytopenia is present (the rest of the blood components are normal) and where other conditions or drugs that may cause thrombocytopenia are not present. [4]

- Thrombocytopenia in ITP is caused by the combination of increased platelet destruction along with inhibition of platelet production due to specific IgG autoantibodies that are produced by B-cells in the immune system. [4]

- A normal platelet count in a healthy person is between 150,000 and 400,000/mm³. The goal of treatment for chronic ITP should be to maintain a safe platelet count, not to achieve a normal platelet count. [5] Risk of spontaneous bleeding increases as platelet counts drops below 20,000/mm³. [6]

- Choosing Wisely®, an evidence-based initiative to promote wise use of medical resources, states that patients with ITP should not be treated in the absence of bleeding or a very low platelet count. Only rarely should patients be treated when platelet counts are above 30,000, such a preparation of surgery or an invasive procedure. Unnecessary treatment exposes patients to potential adverse events and raises the overall cost of care, with unknown clinical benefit. [7]
International consensus guidelines list corticosteroids, IV anti-D, and immune globulin replacement therapy as first-line treatment options for chronic ITP. Treatment for chronic ITP that is refractory to first-line therapies may include azathioprine, cyclosporine, chemotherapy (e.g. cyclophosphamide, vincristine), danazol, dapsone, mycophenolate mofetil, rituximab, and splenectomy. \[8\]

* Around one-third of patients may expect a long-term response from treatment with an oral corticosteroid. Corticosteroids should be rapidly tapered and stopped in patients who fail to respond after 4 weeks. \[9\]

* Up to two-thirds of patients with ITP who undergo splenectomy may achieve a normal platelet count, which is often sustained with no additional therapy. \[9,10\]

Several studies have evaluated rituximab as a therapy for refractory ITP:

* A case series in 25 patients with refractory ITP using a dose of 375 mg/m\(^2\) weekly for four weeks achieved overall response rates in 52% of patients. The patients in the trial failed to respond to 2 to 5 prior treatments, including eight patients who had failed splenectomy. \[3\]

* Sixty patients with chronic ITP and platelets < 30,000/mm\(^3\) received 375 mg/m\(^2\) rituximab weekly for four weeks. At one and two years, 40% and 33% of patients maintained a platelet count of greater than 50,000/mm\(^3\), respectively. \[11\]

* An open-label trial in 103 patients with ITP and platelets < 20,000/mm\(^3\) were randomized to dexamethasone (40 mg orally daily for 4 days) and rituximab (375 mg/m\(^2\)) every week for 4 weeks or dexamethasone alone. A greater proportion of patients in the rituximab treatment arm had platelet counts of at least 50,000/mm\(^3\) at month 6. Multiple courses of corticosteroids (higher doses) have been associated with better results; however, these higher corticosteroid doses were not studied in this trial. \[12\]

**Dermatomyositis/Polymyositis**

Dermatomyositis and polymyositis are idiopathic inflammatory myopathies. Features include muscle weakness, rash (dermatomyositis), elevated serum muscle enzymes (such as CPK) and myopathic changes on electromyography. Other complications may include lung, esophageal, and cardiac disease, as well as an increased risk of malignancy (greater with dermatomyositis). \[13\]

* Both conditions are immune-mediated, but dermatomyositis is predominantly associated with B-cells, while polymyositis is predominantly associated with T-cells. \[13\]

* Initial treatment options include corticosteroids alone or in combination with disease modifying agents (such as azathioprine, methotrexate). First-line treatment for recurrent or refractory disease includes rituximab and intravenous immune globulin. Cyclosporin, tacrolimus, mycophenolate mofetil, cyclophosphamide, and tumor necrosis factor inhibitors, such as etanercept, may also be considered. \[14,15\]

* There is currently no standard therapy for dermatomyositis or polymyositis that is refractory to corticosteroids. Current evidence is limited to low quality clinical trials and case series.

* Several small case series have evaluated rituximab in patients with dermatomyositis and polymyositis. They reported varying levels of response; however, the duration of response lasted up to 36 months. \[16-18\]
- Rituximab has not been studied versus any other treatments in patients with either dermatomyositis or polymyositis.

**Multicentric Castleman’s Disease (Angiofollicular Lymph Node Hyperplasia)**

- Castleman’s disease, also known as angiofollicular lymph node hyperplasia, is a rare lymphoproliferative disease. There are two subtypes, unicentric (UCD) and multicentric (MCD). They are recognized as two distinct diseases. The multicentric form is strongly associated with immunosuppression (e.g. HIV infection) and human herpesvirus 8 (HHV-8) infection and may progress to B-cell plasmablastic lymphoma. [19]

- Symptoms of MCD include fever, weight loss, anemia, fatigue, peripheral lymphadenopathy, hepatomegaly, and cough or dyspnea. Most patients die of fulminant infection, progressive disease, or related malignancies. [19]

- There is currently no standard therapy for MCD. Current evidence regarding its treatment is poor and is based on small case series. [19]
  * Corticosteroids induce a complete response in about 15 to 20% of patients; however, response is usually not durable.
  * Chemotherapy has been used to induce transient remissions; however, disease usually recurs in 2 to 3 weeks after stopping the chemotherapy.
  * Antiviral medications, thalidomide, and interferons have also been used on a case by case basis with some success.

- There have been several small, prospective, uncontrolled trials that study the use of rituximab in MCD. [20]
  * Rituximab given as a follow up to chemotherapy resulted in a sustained remission off treatment for 60 days in 22 (92%) of 24 patients, with 17 patients (71%) in sustained remission without treatment at 1 year.
  * Rituximab used as monotherapy led to resolution of symptoms in 20 out of 21 patients following the fourth infusion and resulted in partial responses and stable disease in 67% and 29% of patients, respectively.

- For UCD, gold standard therapy includes complete resection, with resective or debulking surgery. Rituximab may be used for unresectable disease. [21]

**Multiple Sclerosis**

- The evidence for the use of rituximab in relapsing-remitting multiple sclerosis (RRMS) is limited to one Phase 2 trial and several observational studies. A Cochrane systematic review concluded there is insufficient evidence to efficacy of rituximab as a disease-modifying therapy for the treatment of RRMS.

- Despite the lack of high-quality RCT data, the available data is promising and rituximab (Rituxan) has a well-characterized safety profile, thus use may be considered in certain patients when other treatment options are ineffective or not tolerated. [22]

**Nephrotic Syndrome**

- Nephrotic syndrome refers to a group of clinical and laboratory features of renal disease, specifically the presence of heavy proteinuria (protein excretion > 3.5 g/24 hours), hypoalbuminemia (< 3.0 g/dL), and peripheral edema. Hyperlipidemia and thrombotic disease are also frequently observed. [23]
Minimal change disease (MCD; also called nil disease or lipoid nephrosis) and focal segmental glomerulosclerosis (FSGS) are common causes of nephrotic syndrome in both children and adult. [23]

First-line therapy for nephrotic syndrome is generally immunosuppression with corticosteroids. Second-line therapy varies depending on the underlying cause but may include agents such as cyclosporine, tacrolimus, and mycophenolate mofetil. [24,25]

Rituximab is generally reserved for patients for whom corticosteroids and other immunosuppressive therapies such as those mentioned above have been ineffective. [24,25]

Data is limited for most therapies used to treat nephrotic syndrome and consist mainly of small randomized controlled studies, uncontrolled studies, and observational data. [24,25]

Neuromyelitis Optica (NMO)

Neuromyelitis optica spectrum disorders (NMO, NMOSD; previously known as Devic disease) are characterized by a combination of bilateral optic neuropathy and cervical myelopathy. While both NMOSD and MS are demyelinating diseases they are considered different diseases based on unique immunologic features and differences in imaging features, biomarkers, and neuropathology. [26]

For acute attacks and relapses of NMOSD, treatment usually consists of intravenous glucocorticoids followed soon by plasmapheresis for refractory or progressive symptoms. For prevention of attacks, systemic immunosuppression with agents including azathioprine, mycophenolate mofetil, rituximab, and mitoxantrone has been used, given the evidence that humoral autoimmunity plays a role in the pathogenesis of NMO. [27,28]

Rituximab has been shown to the frequency of NMOSD relapses and neurologic disability based on results from one systematic review. However, the optimal treatment regimen and duration have not been determined and additional long-term safety experience is needed to clarify the role of rituximab as a first-line option. [29]

Refractory Anti-NMDA Receptor Encephalitis [30,31]

Anti-NMDA receptor encephalitis is a specific type of autoimmune encephalitis, diagnosed by detection of IgG antibodies against a subunit of NMDA receptors in serum or CSF. It can be associated with various neurologic and psychiatric symptoms, including cognitive and speech dysfunction, seizures, dyskinesias, altered consciousness, and autonomic instability.

Based on large case series and years of experience in clinical practice, use of immunosuppression therapy is the standard of care, with corticosteroids, IVIG, plasma exchange, cyclophosphamide, or rituximab. IVIG (400 mg/kg/day for 5 days) in combination with high-dose methylprednisolone or plasma exchange may be useful in treating patients with anti-NMDA receptor encephalitis in the first-line setting. Rituximab and/or cyclophosphamide may be of benefit in patients not responding to IVIG and steroids within 10 days. Children are generally managed with monotherapy (cyclophosphamide or rituximab).

There is no evidence to support the use of rituximab in other types of encephalitis, such as acute disseminated encephalomyelitis (ADEM) or paraneoplastic encephalomyelitis.
**Refractory Autoimmune Hemolytic Anemia (AIHA)**

- Autoimmune hemolytic anemia (AIHA) is a form of anemia that results when the body’s immune system destroys the red blood cells. In children, AIHA is usually self-limiting, often arising after a viral infection and disappearing in one to three months. In adults, AIHA is usually chronic. [20]

- Several different therapies have been used in the treatment of AIHA. [20]
  * First-line treatment of AIHA is corticosteroids (e.g. prednisone). A response is usually seen in one to three weeks.
  * Splenectomy is a viable second-line option. Complete or partial responses occur in approximately two-thirds of patients, a substantial number of patients remain in remission without need for medical intervention for years, and the perioperative risk of splenectomy is low. Contraindications to splenectomy include a high risk of venous thromboembolism and massive obesity. [32]
  * Immunosuppressives (e.g. azathioprine) and cytotoxic agents (e.g. cyclophosphamide) are also used. A response to these therapies generally takes a month or more. Intravenous immune globulin has been used in patients who are refractory to both corticosteroids and splenectomy; however, it is only occasionally effective.

- Refractory cases of AIHA have also been treated with monoclonal antibodies such as rituximab. [3,20] The evidence for rituximab in AIHA is based on low quality, single-arm, open-label, studies in small numbers of patients. [3]

- There are no studies that compare rituximab with any other therapies for AIHA.

**Refractory Evan’s Syndrome**

- Evan’s syndrome refers to the combination of both autoimmune hemolytic anemia (AIHA) and immune (idiopathic) thrombocytopenic purpura (ITP). Approximately 15% of these patients may also have autoimmune neutropenia. [20]

- In approximately 50% of cases an underlying condition is associated with the disease (e.g. lymphoproliferative disorders, common variable immunodeficiency). [20]

- There are no systematic or randomized controlled trials that evaluate the treatments for Evan’s syndrome.

- Glucocorticoids, intravenous immune globulin, and splenectomy are typically the first and second-line therapy choices. [20]

- In refractory cases, azathioprine, cyclophosphamide, cyclosporine, danazol, hematopoietic stem cell transplant, mycophenolate, rituximab, and vincristine have been used. [3,20]

- There is no evidence that compares any one of these therapies with another.

**Refractory Myasthenia Gravis** [33]

- There is randomized controlled trial evidence to support the use of IVIG and plasmapheresis for myasthenia gravis refractory standard oral therapies, such as pyridostigmine, azathioprine, cyclosporine, or cyclophosphamide.
Rituximab may be useful in treating select patients with severe myasthenia gravis who fail to respond to other therapies for refractory MG, based on a large number of case reports.

**Refractory Pemphigoid/Refractory Pemphigus**

- Pemphigoid and pemphigus are groups of autoimmune blistering disorders that affect the skin and mucosa. [34,35]
- Systemic corticosteroids are the mainstay of therapy for both pemphigoid and pemphigus disorders, and are effective for most patients. Oral immunomodulatory agents such as azathioprine, mycophenolate mofetil, and dapsone are often used in combination with systemic corticosteroids in an attempt to minimize the risk for adverse effects of long-term, high-dose steroids therapy. Other interventions, including rituximab, IVIG, and cyclophosphamide are typically reserved for patients who fail to respond to these conventional therapies. [36-38] The goal of therapy is induction of remission.
- While some therapies for pemphigoid and pemphigus have been studied in randomized controlled trials, overall, the data is of low quality as many of these were small and/or open-label. [36-38]

**Rheumatoid Arthritis (RA)**

*Rheumatic Conditions – Background*

- Treatments for rheumatic conditions may include non-medical therapies, medications for the management of symptoms, medications that modify the disease course such as oral or biologic disease modifying anti-rheumatic drugs (DMARD), and the first-in-class phosphodiesterase 4 (PDE4) inhibitor apremilast (Otezla), and the Janus kinase (JAK) inhibitor, tofacitinib (Xeljanz).
- Medications to control inflammation such as nonsteroidal antiinflammatory medications (e.g. ibuprofen, indomethacin, and naproxen) and glucocorticoids (oral or injected into the joint) are effective for the management of symptoms, particularly during the early stages of disease.
- Generic, orally administered DMARDs, including methotrexate (MTX), hydroxychloroquine, leflunomide, and sulfasalazine are effective for decreasing symptoms and slowing disease progression, have a proven track record, and have been the standard of care for many years.
  * MTX is considered effective in the treatment of rheumatoid arthritis (RA) and is the standard reference DMARD to which newer oral and biologic DMARDs are compared for efficacy.
  * Generic oral therapies have known potential risks. The management of these risks is well established.
- The biologic agents can also decrease symptoms, help preserve joint functioning, and slow the progression of chronic inflammatory conditions; however, these medications also have significant risks.
- There is no comparative safety data within the biologics class that indicates one medication or mechanism of action is safer than alternatives, including anti-TNFs compared to non-anti-TNF medications.

- In RA, the best response is seen when MTX is used concomitantly with any of the biologics. Infliximab (Remicade) and golimumab (Simponi, Simponi Aria) have been shown to be effective only when used with MTX. Treatment options other than infliximab (Remicade) or golimumab (Simponi, Simponi Aria) should be considered for patients who cannot take MTX.

- Inhibiting PDE4 is a novel mechanism in the treatment of rheumatic conditions. PDE4 is a protein present in immune cells and is associated with inflammation.

- JAK inhibition is a novel mechanism in the treatment of rheumatic conditions. JAKs are enzymes that stimulate hematopoiesis and promote immune cell function.

Rheumatic Conditions – Rheumatoid Arthritis (RA)

- Several biologic and newer oral agents have been shown to be effective in the treatment of RA including the following:
  * Abatacept (Orencia) intravenous and subcutaneous
  * Adalimumab (Humira)
  * Anakinra (Kineret)
  * Etanercept (Enbrel)
  * Certolizumab pegol (Cimzia)
  * Golimumab (Simponi, Simponi Aria)
  * Infliximab (Remicade)
  * Rituximab (Rituxan)
  * Tocilizumab (Actemra) intravenous and subcutaneous
  * Tofacitinib (Xeljanz)

- All of these agents, with the exception of tocilizumab (Actemra) subcutaneous and tofacitinib (Xeljanz) have high quality data in the treatment of RA (see Table 1) and, therefore, can be indirectly compared based on their calculated number needed to treat (NNTs).

- With the exception of anakinra (Kineret), and those products without high quality data, the efficacy of these agents in the treatment of RA is similar.

Efficacy of rituximab in rheumatoid arthritis (RA)

- A randomized, controlled trial evaluated rituximab versus placebo in patients with moderately to severely active RA. The evidence from this trial is of low quality for reasons that include a high proportion of dropouts, failure to include all randomized patients in the efficacy analysis and uncertain blinding procedures. Bias cannot be ruled out. [39,40]

  * Patients in the trial were diagnosed with RA according to American College of Rheumatology (ACR) Criteria and had at least eight swollen and tender joints.
Rituximab was given concomitantly with oral MTX.
All patients enrolled in the trial had an inadequate disease response after at least one tumor necrosis factor inhibitor (TNF-alfa inhibitor).
Efficacy of rituximab was based on at least a 20% improvement in joint pain and stiffness after 6 months of treatment.

A second randomized controlled trial evaluated patients who had ongoing disease after an initial course of rituximab. The quality of evidence from this study was also low. [39]

The approved dose of rituximab in RA is two-1000 mg intravenous infusions separated by two weeks (one course) with a repeat course at 16 to 24 weeks, depending on clinical response. [39] Several unreliable trials have studied different treatment regimens (lower doses and different durations) in both treatment-experienced and newly diagnosed patients in an attempt to identify the optimal dose and duration for this condition. [41-44]

When one TNF inhibitor is ineffective, a second TNF may be effective, given interpatient variability in response to one option over another. However, use of a third TNF is generally not clinically indicated. Use of a medication with a difference mechanism of action is generally indicated.

**Transplant (Solid Organ) Rejection**

- Acute allograft (organ) rejection may be cellular (T-cell mediated) or humoral (antibody mediated).
- Treatment with intravenous immune globulin (IVIG) with or without rituximab prior to transplant (desensitization) may reduce the risk of antibody-mediated rejection in highly sensitized renal transplant patients. [45]
- One small trial (n = 13) compared the efficacy of IVIG versus IVIG plus rituximab for desensitization in highly sensitized patients. Both regimens appeared to be effective. Further studies are needed to define the relative efficacy of the two regimens for long-term benefit. [46]
- Antibody-mediated rejection may also occur outside of the peri-operative period, most commonly within six months of transplant. The diagnosis is confirmed by a renal biopsy. The goal of therapy is early antibody elimination with IVIG, plasmapheresis, or a combination of modalities. [45,47]
- There is no consensus in the clinical guidelines regarding the use of IVIG or rituximab in either prevention or treatment of antibody-mediated rejection. A variety of protocols have been developed; however, these are highly institution-specific. [45,47,48]

**Waldenström’s Macroglobulinemia**

- Waldenström's macroglobulinemia (WM) is a rare condition arising from malignant B-cells. These B-cells strongly express the CD20 antigen. Patients with WM demonstrate lymphoplasmacytic lymphoma in the bone marrow with an IgM monoclonal gammopathy in the blood. [49]
- Symptoms from WM are related to infiltration of hematopoietic tissues (e.g. anemia, lymphadenopathy, splenomegaly) and/or symptoms related to the IgM monoclonal protein in the blood (e.g. hyperviscosity, peripheral neuropathy). [49]
The evidence for all WM therapies is of poor quality due to small numbers of subjects and lack of blinding and comparators. Because of the low quality of evidence and lack of comparative studies there is currently no standard recommended therapy for WM.

Therapy is reserved for patients with symptomatic disease. Choice of treatment is based on patient age, severity of symptoms, eligibility for autologous stem cell transplantation, comorbidities, and patient preference. Treatments may include conventional chemotherapy, bortezomib (Velcade), rituximab, and thalidomide. [50]

Rituximab has been studied as both a single-agent and in combination with other therapies in the treatment of WM. Reported overall response rates in these trials are in the range of 50% to 94%. The overall quality of the evidence for rituximab in WM, as well as other treatment options, is poor for reasons that include lack of comparator group and lack of blinding. [50]

It is not known whether improved response rate corresponds to improved overall survival in patients with WM. [50]

**Wegener’s Granulomatosis/Microscopic Polyangiitis**

Wegener’s granulomatosis and microscopic polyangiitis are classified as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. [51,52]

They are multisystem autoimmune syndromes characterized by inflammation of microscopic vessels, most commonly in the kidneys and airways. [51,52]

The current standard of care is cyclophosphamide with high-dose corticosteroids. Intravenous (IV) cyclophosphamide is the least-costly form of cyclophosphamide for most patients. In addition, IV cyclophosphamide is usually dosed intermittently, “pulse dosing,” every three to four weeks. When using cyclophosphamide, the general approach is to avoid the use of oral cyclophosphamide, which is dosed daily, due to the risk of bladder toxicity (hemorrhagic cystitis). This risk can be lowered with force diuresis, with adequate hydration (fluid intake), either orally or IV, on the days the cyclophosphamide is administered. Although hemorrhagic cystitis is a risk with either formulation of cyclophosphamide, the less frequent dosing with IV cyclophosphamide correlates with a less frequent need for aggressive hydration. [51-53]

Two unreliable randomized trials studied rituximab in the treatment of patients with (ANCA)-associated vasculitis.

* A study in 99 patients compared corticosteroids and either rituximab or cyclophosphamide. The two treatments were found to be similar with regard to inducing remission at 6 months.[51]

* One small trial in 48 patients demonstrated no difference in sustained remission at 12 months in patients treated with corticosteroids and either cyclophosphamide plus rituximab, or cyclophosphamide alone. [52]

OmedaRx performs independent analyses of oncology medications. The OmedaRx analysis and coverage policy may differ from NCCN guidelines.
INVESTIGATIONAL USES

Rituximab has been studied in several non-oncologic/non-hematologic conditions including antiphospholipid antibody syndrome, chronic graft versus host disease, multiple sclerosis, scleroderma, systemic lupus erythematosus (SLE), and Sjögren’s. [3]

Antiphospholipid antibody syndrome (APS)

- Antiphospholipid antibody syndrome (APS) is an autoimmune vascular syndrome, characterized by recurrent thrombotic complications (and associated thrombocytopenia) and pregnancy morbidity. It may present as a primary condition or in the setting of another autoimmune disease, such as lupus (SLE). [54]
- There is no reliable clinical data to support the safety and efficacy of rituximab for antiphospholipid antibody syndrome. Data are limited to case reports and one uncontrolled, non-randomized Phase 2 pilot trial in patients with anticoagulation-resistant manifestations of antiphospholipid antibody syndrome. [54,55]
- Additional evidence is needed to support the use of rituximab for patients with antiphospholipid antibody syndrome and associated complications, including APS-associated thrombocytopenia.

Chronic graft versus host disease (GVHD)

- Current studies of rituximab in chronic graft versus host disease are small and preliminary. Larger well-controlled trials are needed to establish the safety and efficacy of rituximab in this population.

Scleroderma

- Scleroderma may be localized, or systemic (SSc) and manifest as a variety of skin and vascular disorders, due to excess collagen fibers, such as skin thickening, calcinosis, renal disease, interstitial lung disease, arthralgias (due to skin thickening), and inflammatory arthritis. [56]
- There is no conclusive evidence of the safety or efficacy of rituximab for scleroderma. The evidence is limited to case series and one small proof-of-concept trial (n=14). [56,57]
- The standard of care treatment for scleroderma is generally immunosuppressants and corticosteroids, but is dependent on the type of disease manifestation. Inflammatory arthritis associated with systemic sclerosis is generally managed similar to rheumatoid arthritis, with use of oral DMARDs, such as hydroxychloroquine and methotrexate, followed by biologics, such as TNF inhibitors. However, there is insufficient evidence to support the use of rituximab in scleroderma, in the absence of a diagnosis of rheumatoid arthritis.

Systemic lupus erythematosus (SLE)

- A large phase III randomized controlled trial that studied rituximab versus placebo in patients with SLE did not meet its primary endpoint. [58] Additional studies are necessary to demonstrate safety and efficacy in patients with SLE.

Sjögren’s syndrome— Primary Sjögren’s syndrome is an autoimmune disease, characterized by ocular and oral dryness due to decreased salivary and lacrimal gland function, also known as “sicca complex.” Systemic (extraglandular) manifestations may include, but are not limited to, arthralgias, renal disease (interstitial nephritis), neuropathies and fatigue. [59]
- There is insufficient evidence to support the use of rituximab for the treatment of Sjögren’s. The evidence is limited to Phase 2 trials with inconsistent findings. One small, open-label trial (n=15) found an improvement in symptoms. However, a larger Phase 2 trial (n=120) found no improvement in Sjögren’s symptoms or reduction in disease activity with rituximab treatment.

- Sicca symptoms (dry eyes and/or mouth) are usually treated topically (such as artificial tears) or with systemic cholinergic agents, to stimulate secretions. Systemic Sjögren’s is managed with immunosuppressants, such as hydroxychloroquine, methotrexate, and cyclosporine. The evidence for the use of TNF inhibitors, such as infliximab or etanercept, is limited and findings inconsistent.

SAFETY

- Rituximab carries a boxed warning for severe infusion reactions (some fatal), tumor lysis syndrome, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy.

- Serious bacterial, fungal, and new or reactivated viral infections may occur during and for up to one year following completion of rituximab-based therapy.

- Cardiac arrhythmias and bowel obstruction or perforation have also been reported with rituximab therapy.

DOSING and ADMINISTRATION CONSIDERATIONS

- The initial dose of rituximab should be initiated at 50 mg/hr to minimize the risk of infusion reactions. The dose may be increased in 50 mg/hr increments as tolerated to a maximum of 400 mg/hr.

- Premedication with acetaminophen and diphenhydramine is recommended for all patients receiving rituximab. In patients with RA, methylprednisolone 100 mg IV (or equivalent) is also recommended 30 minutes before each infusion.
Table 1. Summary of Evidence Quality by Indication for Select Disease Modifying Anti-Rheumatic Drugs (DMARD)

<table>
<thead>
<tr>
<th>Generic (brand)</th>
<th>[Original FDA-approval Date]</th>
<th>Route/ Site of Administration</th>
<th>Mechanism of action</th>
<th>Rheumatoid Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>infliximab (Remicade)</td>
<td>[8/1998]</td>
<td>IV/HCP</td>
<td>TNF antagonist (anti-TNF)</td>
<td>✓</td>
</tr>
<tr>
<td>etanercept (Enbrel)</td>
<td>[11/1998]</td>
<td>SC/Pat</td>
<td>TNF antagonist (anti-TNF)</td>
<td>✓</td>
</tr>
<tr>
<td>adalimumab (Humira)</td>
<td>[12/2002]</td>
<td>SC/Pat</td>
<td>TNF antagonist (anti-TNF)</td>
<td>✓</td>
</tr>
<tr>
<td>certolizumab pegol (Cimzia)</td>
<td>[4/2008]</td>
<td>SC/Pat</td>
<td>TNF antagonist (anti-TNF)</td>
<td>✓</td>
</tr>
<tr>
<td>golimumab (Simponi)</td>
<td>[4/2009]</td>
<td>SC/Pat</td>
<td>TNF antagonist (anti-TNF)</td>
<td>✓</td>
</tr>
<tr>
<td>golimumab (Simponi Aria)</td>
<td>[7/2013]</td>
<td>IV/HCP</td>
<td>B-lymphocyte depleter</td>
<td>✓</td>
</tr>
<tr>
<td>rituximab (Rituxan)</td>
<td>[11/1997]</td>
<td>IV/HCP</td>
<td>IL-1 receptor antagonist</td>
<td>✓</td>
</tr>
<tr>
<td>anakinra (Kineret)</td>
<td>[11/2001]</td>
<td>SC/Pat</td>
<td>IL-1 receptor antagonist</td>
<td>✓</td>
</tr>
<tr>
<td>canakinumab (Ilaris)</td>
<td>[6/2009]</td>
<td>SC/Pat</td>
<td>IL-18 receptor antagonist</td>
<td>✓</td>
</tr>
<tr>
<td>Sarilumab (Kevzara)</td>
<td>[5/2017]</td>
<td>SC/Pat</td>
<td>IL-6 receptor antagonist</td>
<td>✓</td>
</tr>
<tr>
<td>tocilizumab (Actemra)</td>
<td>[1/2010]</td>
<td>IV/HCP</td>
<td>IL-6 receptor antagonist</td>
<td>✓</td>
</tr>
<tr>
<td>tocilizumab (Actemra)</td>
<td>[10/2013]</td>
<td>SC/Pat</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>ustekinumab (Stelara)</td>
<td>[9/2009]</td>
<td>SC/Pat, HCP</td>
<td>IL-12, -23 receptor antagonist</td>
<td></td>
</tr>
<tr>
<td>natalizumab (Tysabri)</td>
<td>[11/2004]</td>
<td>IV/HCP</td>
<td>Integrin inhibitor</td>
<td></td>
</tr>
<tr>
<td>vedolizumab (Entyvio)</td>
<td>[5/2014]</td>
<td>IV/HCP</td>
<td>Integrin inhibitor</td>
<td></td>
</tr>
<tr>
<td>abatacept (Orencia)</td>
<td>[12/2005]</td>
<td>IV/HCP</td>
<td>T-lymphocyte inhibitor</td>
<td>✓</td>
</tr>
<tr>
<td>abatacept (Orencia)</td>
<td>[12/2011]</td>
<td>SC/Pat</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>tofacitinib (Xeljanz)</td>
<td>[11/2012]</td>
<td>PO/Pat</td>
<td>JAK inhibitor</td>
<td>x</td>
</tr>
<tr>
<td>apremilast (Otezla)</td>
<td>[3/2014]</td>
<td>PO/Pat</td>
<td>PDE-4 inhibitor</td>
<td></td>
</tr>
</tbody>
</table>

HCP = healthcare provider administered; IL = interleukin; IV = intravenous; JAK = Janus kinases; Pat = patient (self) administered; PDE = phosphodiesterase; PO = oral; SC = subcutaneous; TNF = tumor necrosis factor; ✓ = FDA-approved indication and high confidence data; x = FDA-approved indication and less than high confidence data; = not FDA-approved, but specifically recommended by clinical practice guidelines. *

* Refers to data for induction therapy only. Data for maintenance therapy is less than high confidence. **FDA approved, but evidence has not undergone complete appraisal.

* For complete list of branded DMARDs and evidence for efficacy, see “Drugs for Chronic Inflammatory Diseases” at https://www.omedarx.com/files/dru444.pdf
## Appendix 1: B-cell Mediated Cancers and corresponding ICD-9 codes

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>ICD-9 Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>[204.00 to 204.01]</td>
</tr>
<tr>
<td>Central Nervous System Cancers</td>
<td></td>
</tr>
<tr>
<td>Leptomeningeal metastases</td>
<td>[198.4]</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>[200.50 to 200.51]</td>
</tr>
<tr>
<td>Hodgkin Lymphoma – Lymphocyte-predominant</td>
<td>[201.40 to 204.8]</td>
</tr>
<tr>
<td>Non-Hodgkin’s Lymphoma</td>
<td></td>
</tr>
<tr>
<td>AIDS-related B-cell lymphoma</td>
<td>[042 with 200.20 to 200.28, 200.70 to 200.78, 202.80 to 202.88]</td>
</tr>
<tr>
<td>Burkitt’s lymphoma</td>
<td>[200.20 to 200.28]</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia/small lymphocytic lymphoma</td>
<td>[200.10 to 200.18, 204.10, 204.12]</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>[200.70 to 200.78, 202.80 to 202.88]</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>[202.00 to 202.08, 200.30 to 200.38]</td>
</tr>
<tr>
<td>Gastric MALT lymphoma</td>
<td>[200.30 to 200.38]</td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td>[202.40 to 202.48]</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>[200.40 to 200.48]</td>
</tr>
<tr>
<td>Non-gastric MALT lymphoma</td>
<td>[200.30 to 200.38]</td>
</tr>
<tr>
<td>Primary cutaneous B-cell lymphoma</td>
<td>[200.80 to 200.88, 202.80 to 202.88]</td>
</tr>
<tr>
<td>Splenic marginal zone lymphoma</td>
<td>[200.30 to 200.38]</td>
</tr>
</tbody>
</table>

## Appendix 2: American College of Rheumatology (ACR) Classification Criteria for Establishing the Diagnosis of Rheumatoid Arthritis (RA) \(^{62,63}\)

Diagnosis of RA requires the presence of at least 4 of 7 criteria below:

1. Morning stiffness in and around joints lasting more than 1 hour.
2. Arthritis in at least 1 area in a wrist or proximal interphalangeal (PIP) joint (hands or fingers) for > 6 weeks.
3. Simultaneous swelling or fluid accumulation in 3 or more joints for > 6 weeks.
4. Symmetric (bilateral joint) involvement for > 6 weeks.
5. Presence of rheumatoid nodules.
6. Positive serum rheumatoid factor.
7. Radiographic changes typical of RA (erosion or unequivocal bony decalcification in or adjacent to the involved joint) on hand and wrist present.
Appendix 3: American College of Rheumatology (ACR) Assessment Components for Improvement in Rheumatoid Arthritis (RA) [64]

- Tender joint count.
- Swollen joint count.
- Patient's assessment of pain.
- Patient's global assessment of disease activity.
- Physician's global assessment of disease activity.
- Patient's assessment of physical function.
- Acute phase reactant measures (erythrocyte sedimentation rate or C-reactive protein levels.)

Appendix 4: Select List of Oral Non-biologic Disease Modifying Anti-rheumatic Drugs (nbDMARD)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>acitretin (Soriatane)</td>
<td>mercaptopurine (6-MP; Purinethol)</td>
</tr>
<tr>
<td>azathioprine (Imuran)</td>
<td>methotrexate (oral, injectable)</td>
</tr>
<tr>
<td>cyclosporine (Gengraf, Neoral, Sandimmune)</td>
<td>mycophenolate (CellCept, Myfortic)</td>
</tr>
<tr>
<td>hydroxychloroquine (Plaquenil)</td>
<td>sulfasalazine (Azulfidine)</td>
</tr>
<tr>
<td>leflunomide (Arava)</td>
<td>cyclophosphamide (Cytoxan)</td>
</tr>
</tbody>
</table>

Appendix 5: FDA-approved Disease-Modifying Agents Used in the Treatment of Multiple Sclerosis (MS)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>alemtuzumab (Lemtrada®)</td>
<td></td>
</tr>
<tr>
<td>daclizumab (Zinbryta™)</td>
<td></td>
</tr>
<tr>
<td>dimethyl fumarate (Tecfidera®)</td>
<td></td>
</tr>
<tr>
<td>fingolimod (Gilenya®)</td>
<td></td>
</tr>
<tr>
<td>glatiramer acetate (Copaxone®)</td>
<td></td>
</tr>
<tr>
<td>interferon beta-1a (Avonex®, Rebif®)</td>
<td></td>
</tr>
<tr>
<td>interferon beta-1b (Betaseron®, Extavia®)</td>
<td></td>
</tr>
<tr>
<td>mitoxantrone (Novantrone®)</td>
<td></td>
</tr>
<tr>
<td>natalizumab (Tysabri®)</td>
<td></td>
</tr>
<tr>
<td>peginterferon beta-1a (Plegridy®)</td>
<td></td>
</tr>
<tr>
<td>ocrelizumab (Ocrevus®)</td>
<td></td>
</tr>
<tr>
<td>teriflunomide (Aubagio®)</td>
<td></td>
</tr>
</tbody>
</table>
Cross References

| Drugs for chronic inflammatory diseases (including all drugs in Table 1 above), dru444 |
| Arzerra™, ofatumumab dru196 |
| Immune Globulin Replacement Therapy (IVIG, SQ), dru020 |
| Nplate®, romiplostim dru162 |
| Promacta®, eltrombopag dru180 |
| Velcade®, bortezomib dru190 |

Codes

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCPCS</td>
<td>J9310</td>
<td>Injection, rituximab, 100 mg</td>
</tr>
<tr>
<td>HCPCS</td>
<td>n/a</td>
<td>Subcutaneous, rituximab</td>
</tr>
<tr>
<td>ICD-9</td>
<td>238.77</td>
<td>B-cell post-transplant lymphoproliferative disorder</td>
</tr>
<tr>
<td>ICD-9</td>
<td>273.3</td>
<td>Waldenström’s macroglobulinemia</td>
</tr>
</tbody>
</table>

References

1. Rituxan Hycela™ (rituximab and hyaluronidase human) injection, for subcutaneous use [package insert]. South San Francisco, CA: Genentech, Inc.; June 2017


47. Timoptic-XE® (timolol maleate ophthalmic gel-forming solution) [package insert]. Whitehouse Station, NJ: Merck and Co; September 2005


## Revision History

<table>
<thead>
<tr>
<th>Revision Date</th>
<th>Revision Summary</th>
</tr>
</thead>
</table>
| 8/11/2017     | • Add coverage criteria for rituximab/hyaluronidase (Rituxan Hycela) for the indications with evidence for efficacy and safety (diffuse large B-cell lymphoma, follicular lymphoma, and chronic lymphocytic leukemia).  
• Modify RA coverage criteria (delete step therapy with TNFs).  
• Modify MS criteria to mirror criteria language in the other MS drugs for refractory MS |
| 4/14/2017     | • Clarified coverage criteria for:  
  o Castleman’s, to include unicentric disease  
  o Refractory myositis, to align with diagnostic criteria in IVIG policy.  
  o Multiple sclerosis, to align with step therapy criteria in other MS coverage policies  
• Add coverage criteria for:  
  o Refractory anti-NMDA encephalitis  
  o Refractory myasthenia gravis |
| 4/8/2016      | • Merged coverage criteria for Dermatomyositis and Polymyositis to one criterion of “Refractory myositis.”  
• Clarify RRMS criteria for “ineffective” (No change to intent). |
| 12/11/2015    | • Added coverage criteria for refractory multiple sclerosis  
• Removed relapsing forms of multiple sclerosis from investigational uses and clarified that progressive forms of multiple sclerosis are still considered investigational |