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Clinical Guideline

Guideline Number: CG055, Ver. 6

Rituximab (Rituxan) for Multiple Sclerosis and Myasthenia Gravis

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Plan members with certain autoimmune or oncologic conditions may be eligible for treatment with a medication called rituximab (Rituxan), a monoclonal antibody against the CD20 proteins that are expressed by a type of white blood cells (and in some cases, cancerous cells) in the body. This medication has a number of potential adverse effects, including hepatitis B reactivation, infusion reaction, and tumor lysis syndrome, and members receiving it should be under the ongoing care of a physician. There are a number of different formulations as well as biosimilar versions of rituximab. This guideline provides medical necessity criteria for the "off-label" use of rituximab for multiple sclerosis and myasthenia gravis.

This guideline does not address clinical indications for conditions other than multiple sclerosis and myasthenia gravis. For all other indications, please refer to **MCG Rituximab (A-0448)** for medical necessity criteria.

NOTE: The Plan may require that preferred medications be used first. Please review the Plan Clinical Guideline CG052: Preferred Physician-Administered Specialty Drugs for a full list of our preferred and non-preferred drugs.

Definitions

"**Multiple Sclerosis (MS)**" is a long-term (chronic) immune-mediated inflammatory demyelinating disease of the central nervous system. Multiple sclerosis can be categorized as one of the following clinical types:

- "**Clinically Isolated Syndrome (CIS)**" is the first clinical episode that is suggestive of MS occurring with neurological symptoms.
- "**Primary progressive MS**" is characterized by progressive accumulation of disability from disease onset with occasional periods of stability.
- "**Secondary progressive MS**" is characterized by an initial relapsing-remitting course followed by progressive accumulation of disability.
- "**Relapsing-remitting MS**" is the most common type of MS and is characterized by clearly defined relapses followed by periods of remission.

"**Myasthenia gravis**" is a long-term (chronic) condition that happens when the body's infection-fighting system (immune system) attacks certain connections between nerves and muscles by mistake. The proteins (antibodies) made by the immune system block a chemical called acetylcholine, causing problems when the body sends nerve signals to the muscles. This causes weakness in certain muscles such as the ones that control swallowing, eye movement, facial movements, or even those that help with breathing.

"**Relapse**", or exacerbation, refers to a disease that had resolved for a period of at least 6 months but has now recurred.

"**Remission**" refers to a period of partial or full recovery, or disease inactivity.

"Rituximab" (generic for Rituxan) is an intravenous monoclonal antibody medication that binds to the CD20 protein to reduce the ability of the cell to differentiate.

- **"CD20"** refers to a protein present on the surface of a type of white blood cell called the b-lymphocyte.
- **"Monoclonal antibody"** refers to a medication produced from a single cell line or clone of cells ("monoclonal'') with a specific target ("antibody").

Clinical Indications

Medical Necessity Criteria for Initial Authorization

Rituximab (Rituxan) for Multiple Sclerosis

The Plan considers rituximab for multiple sclerosis medically necessary when **ALL** of the following criteria are met:

1. The drug is prescribed by or in consultation with a neurologist; ***AND***
2. The member is 18 years of age or older; ***AND***
3. The member has ONE of the following diagnoses:
    a. Primary progressive MS; ***or***
    b. Secondary progressive MS; ***or***
    c. Relapsing-remitting MS; ***AND***
4. The member does not have ANY of the following contraindications:
    a. Have or have had progressive multifocal leukoencephalopathy (PML) due to rituximab***; or***
    b. Is pregnant or breastfeeding***; or***
    c. John Cunningham Virus***; or***
    d. Known hypersensitivity or severe infusion reaction to rituximab or other components of the medication***; or***
    e. Live virus vaccinations prior to or during rituximab treatment***; or***
    f. Positive Hepatitis B serology or active HBV infection***; or***
    g. Signs or symptoms of severe, active infection (e.g., pneumonia, septic arthritis)***; or***
    h. untreated latent or active tuberculosis

Rituximab (Rituxan) for Myasthenia Gravis

The Plan considers rituximab for myasthenia gravis medically necessary when **ALL** of the following criteria are met:

1. The drug is prescribed by or in consultation with a neurologist; ***AND***
2. The member is 18 years of age or older; ***AND***
3. The member has a documented diagnosis of ONE of the following:
    a. muscle-specific tyrosine kinase (MuSK) antibody positive myasthenia gravis; ***or***
    b. acetylcholine receptor antibody-positive refractory myasthenia gravis AND the member is unable to use, limited by toxicity, or has adequately tried and failed or experienced insufficient response to ALL of the following alternatives:
        i. Cholinesterase inhibitors (eg, pyridostigmine); ***and***

ii. Corticosteroids (e.g., prednisone) or inability to taper steroids below a reasonably acceptable level without return of symptoms; ***and***

iii. Immunosuppressive therapies (e.g., azathioprine, cyclosporine, mycophenolate mofetil, cyclophosphamide, tacrolimus); ***AND***

4. The member does not have ANY of the following contraindications:
    a. Have or have had progressive multifocal leukoencephalopathy (PML) due to rituximab***; or***
    b. Is pregnant or breastfeeding***; or***
    c. John Cunningham Virus***; or***
    d. Known hypersensitivity or severe infusion reaction to rituximab or other components of the medication***; or***
    e. Live virus vaccinations prior to or during rituximab treatment***; or***
    f. Positive Hepatitis B serology or active HBV infection***; or***
    g. Signs or symptoms of severe, active infection (e.g., pneumonia, septic arthritis)***; or***
    h. untreated latent or active tuberculosis

If the above prior authorization criteria are met, Rituximab (Rituxan) will be approved for up to 6-months.

Continued Care

Medical Necessity Criteria for Reauthorization

Requests for continuation of therapy will be approved for up to 12-months when clinical documentation is submitted showing evidence of the drug's effectiveness, including evidence of low disease activity or improvement in signs and symptoms.

Experimental or Investigational / Not Medically Necessary

Rituximab (Rituxan) for any other indications not listed above or outlined in MCG Rituximab (A-0448) criteria is *not* considered medically necessary by the Plan, or it is considered experimental or investigational.

Applicable Billing Codes (HCPCS/CPT Codes)

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*

J9312	Injection, rituximab, 10 mg
ICD-10 codes considered medically necessary if criteria are met:	
Code	*Description*
G35	Multiple sclerosis
G70.00	Myasthenia gravis without (acute) exacerbation
G70.01	Myasthenia gravis with (acute) exacerbation

References

1. Alping P, Frisell T, Novakova L, et al. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. Ann Neurol 2016; 79:950.
2. American Academy of Neurology. Practice Guideline Recommendations Summary: Disease-modifying Therapies for Adults with Multiple Sclerosis. April 2018.
3. Bar-Or A, Calabresi PA, Arnold D, et al. Rituximab in relapsing-remitting multiple sclerosis: A 72-week, open-label, phase I trial. Ann Neurol. 2008;63(3):395-400.
4. Beecher G, Anderson D, Siddiqi ZA. Rituximab in refractory myasthenia gravis: Extended Prospective Study Results. Muscle Nerve. 2018 Sep; 58 (3): 452-455. DOI: 10.1002/mus.26156
5. Castillo-Trivino T, Braithwaite D, Bacchetti P, Waubant E. Rituximab in relapsing and progressive forms of multiple sclerosis: a systematic review. PLoS ONE 2013;8(7):e66308.
6. Chakravarty EF, Murray ER, Kelman A, et al, "Pregnancy Outcomes Following Maternal Exposure to Rituximab," Blood, 2011, 117(5):1499-506.
7. Chitnis T. Disease-modifying therapy of pediatric multiple sclerosis. Neurotherapeutics 2013;10(1):89-96.
8. Ennishi D, Yokoyama M, Terui Y, et al. Does Rituximab Really Induce Hepatitis C Virus Reactivation? American Society of Clinical Oncology Journal. Journal of Clinical Oncology. 2008; 26 (28): 4695-4696. DOI: 10.1200/JCO.2008.18.7609
9. Farmakidis C, Pasnoor M, Dimachkie MM, et al. Treatment of Myasthenia Gravis. Neurol Clin. 2018; 36 (2): 311-337.
10. Fleischmann RM. Safety of biologic therapy in rheumatoid arthritis and other autoimmune diseases: focus on rituximab. Semin Arthritis Rheum 2009; 38:265.
11. Genentech, Inc. Genentech and Biogen Idec announce top-line results from a phase II/III clinical trial of rituxan in primary-progressive multiple sclerosis. Press Releases. South San Francisco, CA: Genentech, Inc.; April 2008.
12. Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016;75(5):795-810.
13. Granqvist M, Boremalm M, Poorghobad A, et al. Comparative Effectiveness of Rituximab and Other Initial Treatment Choices for Multiple Sclerosis. JAMA Neurol 2018; 75:320.
14. Hartung HP, Aktas O. Bleak prospects for primary progressive multiple sclerosis therapy: Downs and downs, but a glimmer of hope. Ann Neurol. 2009;66(4):429-432.

15. Hauser SL, Waubant E, Arnold DL, et al; for the HERMES Trial Group. B-cell depletion with rituximab in relapsing–remitting multiple sclerosis. N Engl J Med. 2008;358(7):676-688.
16. Hawker K, O'Connor P, Freedman MS, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. Ann Neurol 2009; 66:460.
17. He D, Guo R, Zhang F, et al. Rituximab for relapsing-remitting multiple sclerosis. Cochrane Database Syst Rev. 2013;(12):CD009130.
18. Klotz L, Wiendl H. Monoclonal antibodies in neuroinflammatory diseases. Expert Opinion on Biological Therapy 2013;13(6):831-46.
19. Koralnik IJ. Progressive multifocal leukoencephalopathy (PML): Epidemiology, clinical manifestations, and diagnosis. UpToDate.com. https://www.uptodate.com/contents/progressive-multifocal-leukoencephalopathy-pml-epidemiology-clinical-manifestations-and-diagnosis?search=john%20cunningham%20virus&source=search_result&selectedTitle=2~91&usage_type=default&display_rank=2#H601994112 Last updated: July 2021.
20. Li T, Zhang GQ, Li Y, et al. Efficacy and safety of different dosages of rituximab for refractory generalized AChR myasthenia gravis: a meta-analysis. J Clin Neurosci. 2021;85:6-12. doi:10.1016/j.jocn.2020.11.043
21. Lishner M, Avivi I, Apperley JF, et al. Hematologic Malignancies in Pregnancy: Management Guidelines From an International Consensus Meeting. J Clin Oncol. 2016;34(5):501-508.
22. Mitka M. FDA: Increased HBV reactivation risk with ofatumumab or rituximab. JAMA 2013; 310:1664.
23. Naegelin Y, Naegelin P, von Felten S, et al. Association of Rituximab Treatment With Disability Progression Among Patients With Secondary Progressive Multiple Sclerosis. JAMA Neurol 2019; 76:274.
24. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. Neurology 2021; 96:114.
25. Olek MJ, Mowry, E. Treatment of progressive multiple sclerosis in adults. UpToDate. Waltham, MA: UpToDate; reviewed August 2019.
26. Pyrpasopoulou A, Douma S, Vassiliadis T, et al. Reactivation of chronic hepatitis B virus infection following rituximab administration for rheumatoid arthritis. Rheumatol Int 2011; 31:403.
27. Rae-Grant A, Day GS, Marrie RA, et al. Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis. Neurology. 2018;90 (17):789-800.
28. Rituxan (rituximab) [prescribing information]. South San Francisco, CA: Genentech Inc; December 2021.
29. Salzer J, Svenningsson R, Alping P, et al. Rituximab in multiple sclerosis: a retrospective observational study on safety and efficacy. Neurology. 2016;87(20):2074-2081. doi:10.1212/WNL.0000000000003331
30. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. Neurology. 2016;87(4). doi:https://n.neurology.org/content/87/4/419.long
31. Scotti B, Disanto G, Sacco R, et al. Effectiveness and safety of Rituximab in multiple sclerosis: an observational study from Southern Switzerland. PLoS ONE 2018;13(5): e0197415.
32. Tandan R, Hehir MK 2nd, Waheed W, Howard DB. Rituximab treatment of myasthenia gravis: a systematic review. Muscle Nerve. 2017;56(2):185-196.
33. Tien YC, Yen HH, Chiu YM. Incidence and clinical characteristics of hepatitis B virus reactivation in HBsAg-negative/HBcAb-positive patients receiving rituximab for rheumatoid arthritis. Clin Exp Rheumatol 2017; 35:831.

34. Topakian R, Zimprich F, Iglseder S, et al. High efficacy of rituximab for myasthenia gravis: a comprehensive nationwide study in Austria. J Neurol. 2019;266(3):699-706. doi:10.1007/s00415-019-09191-6
35. Whittam DH, Tallantyre EC, Jolles S, et al. Rituximab in neurological disease: principles, evidence and practice. Pract Neurol 2019; 19:5.
36. Yamout B, et al. Consensus guidelines for the diagnosis and treatment of multiple sclerosis. Current Medical Research and Opinion 2013;29(6):611-21.
37. Yamout BI, El-Ayoubi NK, Nicolas J, El Kouzi Y, Khoury SJ, Zeineddine MM. Safety and efficacy of rituximab in multiple sclerosis: a retrospective observational study. J Immunol Res. 2018;2018:9084759. doi:10.1155/2018/9084759

Clinical Guideline Revision / History Information

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