

Ocrelizumab (Ocrevus, Ocrevus Zunovo)

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

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system. It typically presents in young adults (generally diagnosed before 50 years of age) with symptoms such as vision problems, muscle weakness, numbness, and difficulty with balance and coordination. The most common form is relapsing-remitting MS (occurring in about 85% of patients), characterized by acute attacks followed by periods of remission. Treatment goals include reducing relapses, slowing disability progression, and managing symptoms. Disease-modifying therapies (DMTs) are the primary treatment approach and include injectable medications (e.g., interferons, glatiramer acetate), oral medications (e.g., dimethyl fumarate, fingolimod, teriflunomide, etc.), and infusion therapies (e.g., natalizumab, ocrelizumab).

Ocrelizumab is a humanized monoclonal antibody that selectively targets CD20-positive B cells. It is approved for:

- Relapsing forms of MS (including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease).
- Primary progressive MS (PPMS).

Ocrelizumab is available in two formulations:

1. Ocrevus: Intravenous (IV) formulation.
2. Ocrevus Zunovo: Subcutaneous (SC) formulation containing ocrelizumab and hyaluronidase-ocsq.

Definitions

"Clinically isolated syndrome" refers to a first episode of neurologic symptoms lasting at least 24 hours caused by inflammation or demyelination in the central nervous system.

"Compendia" are summaries of drug information and medical evidence to support decision-making about the appropriate use of drugs and medical procedures. Examples include, but are not limited to:

1. American Hospital Formulary Service Drug Information
2. Clinical pharmacology
3. National Comprehensive Cancer Network Drugs and Biologics Compendium
4. Thomson Micromedex DrugDex
5. United States Pharmacopeia-National Formulary (USP-NF)

"Disease-modifying therapy" is a medication that modifies the course of MS by reducing relapses and slowing disability progression.

"EDSS" or "Expanded Disability Status Scale" refers to the most widely utilized MS assessment tool that consists of an ordinal clinical rating scale with half point increments ranging from 0 (normal neurologic examination) to 10 (death due to MS).

"Multiple sclerosis" is a chronic autoimmune disease of the central nervous system characterized by inflammation, demyelination, and neurodegeneration.

"Primary Progressive MS (PPMS)" is a form of MS characterized by worsening neurologic function from the onset of symptoms, without early relapses or remissions.

"Relapse" is defined as the appearance of new symptoms or the worsening of existing symptoms lasting at least 24 hours in the absence of fever or infection.

"Relapsing-remitting MS" refers to a disease course characterized by clearly defined attacks of new or increasing neurologic symptoms followed by periods of partial or complete recovery.

"Secondary progressive MS" is a disease course following relapsing-remitting MS that is characterized by a progressive worsening of neurologic function over time with or without relapses.

Medical Necessity Criteria for Initial Authorization

The Plan considers Ocrelizumab (Ocrevus, Ocrevus Zunovo) medically necessary when recent (within the last 3 months) clinical chart documentation provided indicates the member meets ALL of the following:

1. Prescribed by or in consultation with a neurologist or physician who specializes in the treatment of multiple sclerosis; *AND*
2. Is 18 years of age or older; *AND*
3. Patient has ONE of the following diagnoses:
 - a. Relapsing form of multiple sclerosis (including relapsing-remitting MS, active secondary progressive MS, or clinically isolated syndrome); *or*
 - b. Primary progressive multiple sclerosis (PPMS); *AND*
4. The member meets ONE of the following criteria:
 - a. For relapsing forms of MS the member meets ONE of the following:
 - i. Documentation of highly active or aggressive disease, as demonstrated by at least ONE of the following:
 1. Frequent relapses (≥ 2 in the past year); *or*
 2. At least 1 relapse with incomplete recovery and MRI activity; *or*
 3. Rapidly advancing disability or cognitive impairment; *or*
 4. Disabling relapse with suboptimal response to corticosteroids; *or*
 5. MRI findings showing high disease activity (e.g., new/enlarging T2 lesions, enhancing lesions); *or*
 - ii. Is unable to use, or has tried and failed at least ONE of the following:
 1. Dimethyl Fumarate (generic Tecfidera); *and/or*
 2. Fingolimod (generic Gilenya); *or*
 - b. For primary progressive MS the member meets ALL of the following:
 - i. Evidence of disability progression independent of relapses over the past year;
and
 - ii. Expanded Disability Status Scale (EDSS) Score of ≤ 6.5 ; *AND*
5. Has been screened for hepatitis B virus *AND* does not have active infection; *AND*
6. Ocrelizumab (Ocrevus, Ocrevus Zunovo) will be used as monotherapy for multiple sclerosis (i.e., member is not using and will not use other disease-modifying MS therapies while on Ocrelizumab); *AND*
7. Ocrelizumab (Ocrevus, Ocrevus Zunovo) is being prescribed within the manufacturer's published dosing guidelines or falls within dosing guidelines found in a compendia of current literature.
 - o *For Ocrevus (IV):*
 - o *Initial doses: 300 mg IV infusion, followed two weeks later by a second 300 mg IV infusion.*
 - i. *Initial authorization: Up to 600 mg in the first 28 days.*
 - o *Subsequent doses: 600 mg intravenous infusion every 6 months.*
 - i. *Up to 600 mg every 6 months.*
 - o *For Ocrevus Zunovo (SC): 920 mg ocrelizumab/23,000 units hyaluronidase administered as a single 23 mL subcutaneous injection in the abdomen every 6 months.*

If the above prior authorization criteria are met, the requested medication will be approved for up to 12 months.

Medical Necessity Criteria for Reauthorization

Reauthorization for up to 12 months will be granted if the member has recent (within the last 6-months) clinical documentation showing BOTH of the following:

1. The requested medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; *AND*
2. The member has experienced at least ONE of the following:
 - a. Improvement in at least ONE objective measure, such as:
 - i. Reduced disease activity on MRI; *and/or*
 - ii. Improved or stable disability scores; *and/or*
 - iii. Reduced relapse rate; *and/or*
 - iv. Improved fatigue or walking assessments; *AND/OR*
 - b. The member has shown stabilization or improvement in at least ONE MS symptom, such as:
 - i. Motor function; *and/or*
 - ii. Fatigue; *and/or*
 - iii. Vision; *and/or*
 - iv. Bowel/bladder function; *and/or*
 - v. Spasticity; *and/or*
 - vi. Walking/gait; *and/or*
 - vii. Pain/numbness/tingling.

Experimental or Investigational / Not Medically Necessary

Ocrelizumab (Ocrevus, Ocrevus Zunovo) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Use in combination with other disease-modifying therapies for MS.
- The treatment of other autoimmune conditions not specified in the FDA-approved indications (e.g., lupus nephritis, autoimmune encephalitis).
- Use in pediatric members (under 18 years of age).

Applicable Billing Codes (HCPCS/CPT Codes)

Service(s) name

CPT/HCPCS Codes considered medically necessary if criteria are met:	
<i>Code</i>	<i>Description</i>
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
J2350	Injection, ocrelizumab, 1 mg
J2351	Injection, ocrelizumab, 1 mg and hyaluronidase-ocsq
ICD-10 codes considered medically necessary if criteria are met:	
<i>Code</i>	<i>Description</i>
G35	Multiple sclerosis

References

1. Bainbridge JL, Miravalle A, Wong PS. Multiple Sclerosis. In DiPiro JT, Yee GC, Posey LM, et al, eds. Pharmacotherapy: A Pathophysiologic Approach. 11th ed. New York, NY: McGraw-Hill; 2019.
2. Burt RK, Balabanov R, Burman J, Sharrack B, Snowden JA, Oliveira MC, Fagius J, Rose J, Nelson F, Barreira AA, Carlson K, Han X, Moraes D, Morgan A, Quigley K, Yaung K, Buckley R, Alldredge C, Clendenan A, Calvario MA, Henry J, Jovanovic B, Helenowski IB. Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients With Relapsing-Remitting Multiple Sclerosis: A Randomized Clinical Trial. JAMA. 2019 Jan 15;321(2):165-174. doi: 10.1001/jama.2018.18743. PMID: 30644983; PMCID: PMC6439765.
3. Cerqueira JJ, Berthele A, Cree BAC, et al,. Long-Term Treatment With Ocrelizumab in Patients With Early-Stage Relapsing MS: Nine-Year Data From the OPERA Studies Open-Label Extension. Neurology. 2025 Feb 25;104(4):e210142. doi: 10.1212/WNL.0000000000210142. Epub 2025 Jan 30.
4. FDA approves Ocrevus Zunovo as the first and only twice-a-year 10-minute subcutaneous injection for people with relapsing and progressive multiple sclerosis. News release. Genentech. September 13, 2024. Accessed November 14, 2024. <https://www.gene.com/media/press-releases/15036/2024-09-13/fda-approves-ocrevus-zunovo-as-the-first>
5. Freedman MS, Devonshire V, Duquette P, Giacomini PS, Giuliani F, Levin MC, Montalban X, Morrow SA, Oh J, Rotstein D, Yeh EA; Canadian MS Working Group. Treatment Optimization in Multiple Sclerosis: Canadian MS Working Group Recommendations. Can J Neurol Sci. 2020 Jul;47(4):437-455. doi: 10.1017/cjn.2020.66. Epub 2020 Apr 6. PMID: 32654681.
6. Hartung HP, Benedict RHB, Berger T, et al,. Ocrelizumab in Early-Stage Relapsing-Remitting Multiple Sclerosis: The Phase IIIb ENSEMBLE 4-Year, Single-Arm, Open-Label Trial. Neurology. 2024 Dec 24;103(12):e210049. doi: 10.1212/WNL.0000000000210049. Epub 2024 Dec 3.

7. Hauser SL, Bar-Or A, Comi G et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. *N Engl J Med*. 2017; 376:221-234.
8. Hauser, S., & Cree, B. (2020). Treatment of Multiple Sclerosis: A Review.. *The American journal of medicine*. <https://doi.org/10.1016/j.amjmed.2020.05.042>.
9. Li H, Hu F, Zhang Y, Li K. Comparative efficacy and acceptability of disease-modifying therapies in patients with relapsing-remitting multiple sclerosis: a systematic review and network meta-analysis. *J Neurol*. 2020 Dec;267(12):3489-3498. doi: 10.1007/s00415-019-09395-w. Epub 2019 May 25.
10. Lublin FD, Reingold SC, Cohen JA et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014; 83:278-86.
11. Lublin FD, Reingold SC, Cohen JA et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014; 83:278-86.
12. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and Treatment of Multiple Sclerosis: A Review. *JAMA*. 2021;325(8):765–779. doi:10.1001/jama.2020.26858
13. Montalban X, Hauser SL, Kappos L et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. *N Engl J Med*. 2017; 376:209-220.
14. Multiple Sclerosis Society of Canada. Disease-modifying therapies. <https://mssociety.ca/managing-ms/treatments/medications/disease-modifying-therapies-dmts>.
15. National MS Society. Disease-modifying therapies for MS (updated March 2022). Available from National MS Society website: <https://nms2cdn.azureedge.net/cmssite/nationalmssociety/media/msnationalfiles/brochures/brochure-the-ms-disease-modifying-medications.pdf>.
16. Newsome S, Krzystanek E, Selmaj K, et al. OCARINA II, phase III study: results of subcutaneous ocrelizumab administration in patients with multiple sclerosis (S31.006). *Neurology*. Published online April 9, 2024. doi:10.1212/WNL.000000000020524
17. Ocrevus (ocrelizumab) [prescribing information]. South San Francisco, CA: Genentech Inc; January 2024.
18. Ocrevus Zunovo (ocrelizumab and hyaluronidase) [prescribing information]. South San Francisco, CA: Genentech Inc; September 2024.
19. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90(17):777-788.
20. Reich DS, Lucchinetti CF, Calabresi PA. 2018. Multiple sclerosis. *New England Journal of Medicine* 378(2):169-180.
21. Rindi LV, Zaçe D, Braccialarghe N, et al.,. Drug-Induced Progressive Multifocal Leukoencephalopathy (PML): A Systematic Review and Meta-Analysis. *Drug Saf*. 2024 Apr;47(4):333-354. doi: 10.1007/s40264-023-01383-4. Epub 2024 Feb 7.
22. Samjoo IA, Drudge C, Walsh S, et al.,. Comparative efficacy of therapies for relapsing multiple sclerosis: a systematic review and network meta-analysis. *J Comp Eff Res*. 2023 Jul;12(7):e230016. doi: 10.57264/ceer-2023-0016. Epub 2023 Jun 2.
23. Śladowska K, Kawalec P, Holko P, Osiecka O. Comparative safety of high-efficacy disease-modifying therapies in relapsing-remitting multiple sclerosis: a systematic review and network meta-analysis. *Neurol Sci*. 2022 Sep;43(9):5479-5500. doi: 10.1007/s10072-022-06197-3. Epub 2022 Jun 17.
24. Sui Z, Zhu H, Luo J, Yu J, Li L, Zheng Q. Quantitative comparison of the efficacy of clinical drug treatments for primary progressive multiple sclerosis. *J Clin Neurosci*. 2023 Jul;113:45-53. doi: 10.1016/j.jocn.2023.04.003. Epub 2023 May 11.
25. The use of disease-modifying therapies in multiple sclerosis: principles and current evidence summary. Multiple Sclerosis Coalition. Available from the National MS Society Website: <https://www.nationalmssociety.org/>.
26. Tramacere I, Del Giovane C, Salanti G, et al. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *Cochrane Database Syst Rev* 2015;9:CD011381.

27. Vermersch P, Oreja-Guevara C, Siva A, et al,. Efficacy and safety of ocrelizumab in patients with relapsing-remitting multiple sclerosis with suboptimal response to prior disease-modifying therapies: A primary analysis from the phase 3b CASTING single-arm, open-label trial. *Eur J Neurol.* 2022 Mar;29(3):790-801. doi: 10.1111/ene.15171. Epub 2021 Nov 25.
28. Wolinsky JS, Vermersch P, Hartung HP, et al. Sustained reduction in 48-week confirmed disability progression in patients with PPMS treated with ocrelizumab in the ORATORIO OLE: 8-year follow-up. *Multiple Sclerosis Journal.* 2021;27:2S(101-102).
29. Wolinsky JS, Arnold DL, Brochet B et al. Long-term follow-up from the ORATORIO trial of ocrelizumab for primary progressive multiple sclerosis: a post-hoc analysis from the ongoing open-label extension of the randomised, placebo-controlled, phase 3 trial. *Lancet Neurol.* 2020; 19:998-1009.
30. Wu X, Tan X, Zhang J, et al,. The Efficacy and Safety of Anti-CD20 Antibody Treatments in Relapsing Multiple Sclerosis: A Systematic Review and Network Meta-analysis. *CNS Drugs.* 2022 Nov;36(11):1155-1170. doi: 10.1007/s40263-022-00961-x. Epub 2022 Oct 16.
31. Yang, J., Rempe, T., Whitmire, N., Dunn-Pirio, A., & Graves, J. (2022). Therapeutic Advances in Multiple Sclerosis. *Frontiers in Neurology*, 13. <https://doi.org/10.3389/fneur.2022.824926>.

Clinical Guideline Revision / History Information

Original Date: 06/27/2024

Reviewed/Revised: 8/29/2024, 12/02/2024, 10/01/2025