Policy Number	RX501.085
Policy Effective Date	11/15/2024

Ocrelizumab or Ocrelizumab and Hyaluronidase-ocsq

Table of Contents
Coverage
Policy Guidelines
Description
Rationale
Coding
References
Policy History

Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted

study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Ocrelizumab (Ocrevus®) or ocrelizumab and hyaluronidase-ocsq (Ocrevus Zunovo™) **may be considered medically necessary** for the treatment of adults with:

- Relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, or
- Primary progressive multiple sclerosis (PPMS), **AND**

When meeting ALL of the following criteria:

- Hepatitis B virus (HBV) screening demonstrating that the patient is negative for active HBV,
- Absence of active infection,
- Not used in combination with another multiple sclerosis (MS) disease modifying agent, and
- Not given concurrently with live vaccines. All immunizations should be administered according to immunization guidelines at least 4 weeks prior to initiation of treatment.

Ocrelizumab (Ocrevus) or ocrelizumab and hyaluronidase-ocsq (Ocrevus Zunovo™) **is considered experimental, investigational and/or unproven** for all other indications.

Policy Guidelines

None.

Description

Ocrelizumab (Ocrevus) is an immune-suppressing humanized monoclonal antibody designed to target CD20 B-cell surface antigens. The precise mechanism by which ocrelizumab exerts its therapeutic effects in multiple sclerosis (MS) is unknown, but is presumed to involve binding to CD20, a cell surface antigen present on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ocrelizumab results in antibody-dependent cellular cytolysis and complement-mediated lysis. Ocrelizumab can potentially alter the course of disease by lessening the frequency of relapses and disease progression.

Ocrelizumab (Ocrevus) is considered a disease modifying multiple sclerosis treatment. Other disease modifying multiple sclerosis treatments for relapsing forms of MS may include alemtuzumab (Lemtrada), interferon beta products (Avonex®, Rebif®, Betaseron®, Extavia®, Plegridy®), fingolimod (Gilenya®), glatiramer acetate (Copaxone®), teriflunomide (Aubagio®), and dimethyl fumarate (Tecfidera®) - this is not an all-inclusive list.

Multiple Sclerosis (MS)

Multiple sclerosis is a disorder of the central nervous system (CNS) characterized by inflammation, demyelination, and degenerative changes. Most people with MS experience relapses and remissions of neurological symptoms, particularly early in the disease, and clinical events are usually associated with areas of CNS inflammation. Gradual worsening or progression, with or without subsequent acute attacks of inflammation or radiological activity, may take place early, but usually becomes more prominent over time. While traditionally viewed as a disease of only CNS white matter, more advanced imaging techniques have demonstrated significant early and ongoing CNS gray matter damage as well.

Those diagnosed with MS may have many fluctuating and disabling symptoms (including, but not limited to, fatigue, impaired mobility, mood and cognitive changes, pain and other sensory problems, and visual disturbances), resulting in a significant impact on quality of life for patients and their families. (3)

Multiple sclerosis disease courses and their descriptions include the following (1):

- Clinically isolated syndrome (CIS) - is described as a first episode of inflammatory demyelination in the central nervous system that could become MS if dissemination in time and space are established.
- Relapsing-remitting MS (RRMS) – includes episodes of acute worsening of neurologic functioning (new symptoms or worsening of existing symptoms) with total or partial recovery and no apparent progression of disease.
- Primary progressive MS (PPMS) – includes steadily worsening neurologic function (accumulation of disability) from the onset of symptoms without initial relapses of remission.
- Secondary progressive MS – described as following an initial relapsing-remitting course, the disease becomes more steadily progressive, with or without relapses. The term active indicates showing evidence of new relapses, new gadolinium-enhancing lesions and/or new enlarging T2 lesions on magnetic resonance imaging (MRI) over a specified time.

Regulatory Status

On March 28, 2017, ocrelizumab received Food and Drug Administration (FDA) approval as a therapy for individuals with primary progressive and relapsing forms of multiple sclerosis. (2)

In July 2019, ocrelizumab labelled indications were expanded to address relapsing forms of multiple sclerosis to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults. (4)

Ocrelizumab (Ocrevus) is an intravenously infused medication. The starting dose is 300 mg given on day one followed by 300 mg two weeks later. Thereafter, ocrelizumab (Ocrevus) is given every 6 months at a dose of 600 mg. (5)

The prescribing information for ocrelizumab includes a Warning and Precautions section that contains information on: (5)

- Reducing the risk of infusion reactions and managing infusion reactions,
- Infections and delaying ocrelizumab administration in patients with active infection until the infection is resolved. Vaccination with live-attenuated or live vaccines is not recommended during treatment and until B-cell repletion,
- Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients with MS treated with Ocrevus in the post-marketing setting. Treatment with Ocrevus should be withheld at the first sign or symptom suggestive of PML,
- Monitoring of quantitative serum immunoglobulin levels before, during, and after discontinuation of treatment,
- An increased risk of malignancy may exist, and
- Immune-mediated colitis, which can present as a severe and acute-onset form of colitis, has been reported in patients receiving Ocrevus in the post-marketing setting. Monitor patients for new or persistent diarrhea or other gastrointestinal symptoms and evaluate promptly if colitis is suspected.

In addition to serum immunoglobulin monitoring, Hepatitis B virus screening is indicated prior to starting treatment. Furthermore, Hepatitis B reactivation has been reported in MS patients treated with ocrelizumab in the post-marketing setting.

On September 13, 2024, the FDA approved Ocrevus Zunovo™ (ocrelizumab and hyaluronidase-ocsq) for individuals with primary progressive and relapsing forms of multiple sclerosis. (6) Ocrevus Zunova combines Ocrevus with a proprietary recombinant human hyaluronidase, an enzyme that locally and temporarily degrades hyaluronan in the subcutaneous space, increasing the permeability of the tissue under the skin. This increase in permeability allows Ocrevus to enter and enables it to be rapidly dispersed and absorbed into the bloodstream. Ocrevus Zunovo is administered by a healthcare professional only twice a year via a ten minute subcutaneous injection. (7)

Rationale

This policy was developed in 2017 and is based on the U.S. Food and Drug Administration (FDA) labeled indications as of September 19, 2024.

Ocrelizumab (Ocrevus®)

Relapsing Forms of Multiple Sclerosis

The FDA approval of ocrelizumab for relapsing multiple sclerosis (RMS) was based on two identically designed double-blind, double-dummy randomized controlled trials. (4) The efficacy of ocrelizumab was demonstrated in patients with RMS treated for 96 weeks (Study 1 and Study 2). The dose of Ocrevus was 600 mg every 24 weeks (initial treatment was given as two 300 mg intravenous (IV) infusions administered 2 weeks apart, and subsequent doses were administered as a single 600 mg IV infusion) and placebo subcutaneous injections were given 3 times per week. The dose of Rebif, the active comparator, was 44 mcg given as subcutaneous injections 3 times per week and placebo IV infusions were given every 24 weeks. Both studies

included patients who had experienced at least one relapse within the prior year, or two relapses within the prior two years, and had an Expanded Disability Status Scale (EDSS) score from 0 to 5.5. Patients with primary progressive forms of multiple sclerosis (MS) were excluded. Neurological evaluations were performed every 12 weeks and at the time of a suspected relapse. Brain magnetic resonance imaging (MRI)s were performed at baseline and at Weeks 24, 48, and 96.

The primary outcome of both Study 1 and Study 2 was the annualized relapse rate (ARR). Additional outcome measures included the proportion of patients with confirmed disability progression, the mean number of MRI T1 gadolinium (Gd)-enhancing lesions at Weeks 24, 48, and 96, and new or enlarging MRI T2 hyperintense lesions. Progression of disability was defined as an increase of 1 point or more from the baseline EDSS score attributable to MS when the baseline EDSS score was 5.5 or less, or 0.5 points or more when the baseline EDSS score was above 5.5. Disability progression was considered confirmed when the increase in the EDSS was confirmed at a regularly scheduled visit 12 weeks after the initial documentation of neurological worsening. The primary population for analysis of confirmed disability progression was the pooled population from Studies 1 and 2. (4)

In Study 1, 410 patients were randomized to Ocrevus and 411 to Rebif; 11% of Ocrevus-treated and 17% of Rebif-treated patients did not complete the 96-week double-blind treatment period. The baseline demographic and disease characteristics were balanced between the two treatment groups. At baseline, the mean age of patients was 37 years; 66% were female. The mean time from MS diagnosis to randomization was 3.8 years, the mean number of relapses in the previous year was 1.3, and the mean EDSS score was 2.8; 74% of patients had not been treated with a non-steroid therapy for MS in the 2 years prior to the study. At baseline, 40% of patients had one or more T1 Gd-enhancing lesions (mean 1.8). (4)

In Study 2, 417 patients were randomized to Ocrevus and 418 to Rebif; 14% of Ocrevus-treated and 23% of Rebif-treated patients did not complete the 96-week double-blind treatment period. The baseline demographic and disease characteristics were balanced between the two treatment groups. At baseline, the mean age of patients was 37 years; 66% were female. The mean time from MS diagnosis to randomization was 4.1 years, the mean number of relapses in the previous year was 1.3, and the mean EDSS score was 2.8; 74% of patients had not been treated with a non-steroid therapy for MS in the 2 years prior to the study. At baseline, 40% of Ocrevus-treated patients had one or more T1 Gd-enhancing lesions (mean 1.9). In Study 1 and Study 2, Ocrevus significantly lowered the annualized relapse rate and the proportion of patients with disability progression confirmed at 12 weeks after onset compared to Rebif. (4)

Primary Progressive Multiple Sclerosis

Approval for primary progressive MS (PPMS) was based on a randomized, double-blind, placebo-control (Study 3) clinical trial in patients with PPMS. Patients were randomized 2:1 to receive either Ocrevus 600 mg or placebo as two 300 mg intravenous infusions 2 weeks apart every 24 weeks for at least 120 weeks. Selection criteria required a baseline EDSS of 3 to 6.5 and a score of 2 or greater for the EDSS pyramidal functional system due to lower extremity

findings. Neurological assessments were conducted every 12 weeks. An MRI scan was obtained at baseline and at Weeks 24, 48, and 120. (4)

The primary outcome was the time to onset of disability progression attributable to MS confirmed to be present at the next neurological assessment at least 12 weeks later. Disability progression occurred when the EDSS score increased by 1 point or more from the baseline EDSS if the baseline EDSS was 5.5 points or less, or by 0.5 points or more if the baseline EDSS was more than 5.5 points. In Study 3, confirmed disability progression also was deemed to have occurred if patients who had onset of disability progression discontinued participation in the study before the next assessment. Additional outcome measures included timed 25-foot walk, and percentage change in T2 hyperintense lesion volume. Study 3 randomized 488 patients to Ocrevus and 244 to placebo; 21% of Ocrevus-treated patients and 34% of placebo-treated patients did not complete the trial. The baseline demographic and disease characteristics were balanced between the two treatment groups. At baseline, the mean age of patients was 45; 49% were female. The mean time since symptom onset was 6.7 years, the mean EDSS score was 4.7 and 26% had one or more T1 Gd-enhancing lesions at baseline; 88% of patients had not been treated previously with a non-steroid treatment for MS. The time to onset of disability progression confirmed at 12 weeks after onset was significantly longer for Ocrevus-treated patients than for placebo-treated patients. (4)

In the overall population in Study 3, the proportion of patients with 20 percent worsening of the timed 25-foot walk confirmed at 12 weeks was 49% in Ocrevus-treated patients compared to 59% in placebo-treated patients (25% risk reduction). (4)

In exploratory subgroup analyses of Study 3, the proportion of female patients with disability progression confirmed at 12 weeks after onset was similar in Ocrevus-treated patients and placebo-treated patients (approximately 36% in each group). In male patients, the proportion of patients with disability progression confirmed at 12 weeks after onset was approximately 30% in Ocrevus-treated patients and 43% in placebo-treated patients. Clinical and MRI endpoints that generally favored Ocrevus numerically in the overall population, and that showed similar trends in both male and female patients, included annualized relapse rate, change in T2 lesion volume, and number of new or enlarging T2 lesions. (4)

Ocrelizumab and hyaluronidase-ocsq (Ocrevus Zunovo™)
Studies 1-3 (described above), which established the effectiveness of ocrelizumab for the treatment of RMS and PPMS in adults, were conducted with intravenously-administered ocrelizumab. Study 4 demonstrated comparable exposure of Ocrevus Zunovo relative to the ocrelizumab intravenous formulation, which established the efficacy of Ocrevus Zunovo. (6)

Study 4 was a multicenter, randomized, open-label, parallel arm trial conducted to evaluate the comparative bioavailability, pharmacokinetics, pharmacodynamics, safety, and immunogenicity of Ocrevus Zunovo compared with intravenous ocrelizumab in patients with either RMS or PPMS (NCT05232825). Study 4 enrolled 236 patients (213 with RMS, 23 with PPMS), 18-65 years of age with an EDSS between 0 to 6.5 at screening. The demographics were similar and

baseline characteristics were balanced across the two treatment groups. The mean age was 40 years in both groups. In the Ocrevus Zunovo group, 35% of patients were male and the mean/median duration since MS diagnosis was 5.7/3.1 years, compared to 41% male and 4.8/2.4 years in the ocrelizumab IV group. (6) At Week 12, the geometric mean ratio (90% confidence interval [CI]) for area under the concentration-time curve (AUC) of Ocrevus Zunovo versus Ocrevus was 1.29 (1.23–1.35). Ocrevus Zunovo resulted in near-complete suppression of MRI and relapse activity up to Week 24 was similar to Ocrevus. In both cohorts, ocrelizumab treatment led to rapid and sustained B-cell depletion. The safety profile of Ocrevus Zunovo was consistent with that of Ocrevus; both were well tolerated. No new safety concerns were identified in addition to the known risks associated with ocrelizumab or subcutaneous administration. No ocrelizumab-antidrug antibodies or antibodies to recombinant human hyaluronidase were detected. Investigators concluded that Ocrevus Zunovo demonstrated non-inferiority to Ocrevus with respect to AUC and had similar clinical and imaging measures. Subcutaneous administration of ocrelizumab provides treatment flexibility and additional treatment options for patients and healthcare providers. (8)

Summary of Evidence

Based on the Food and Drug Administration (FDA) label approval, ocrelizumab (Ocrevus) and ocrelizumab and hyaluronidase-ocsq (Ocrevus Zunovo) are considered medically necessary for the treatment of adult patients with relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease; or primary progressive multiple sclerosis (PPMS), when the noted Coverage criteria are met.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J2350, J3490, J3590, J9999

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

References

1. The Use of Disease-Modifying Therapies in Multiple Sclerosis: Principles and Current Evidence. A Consensus Paper by the Multiple Sclerosis Coalition 2019: The Multiple Sclerosis

Coalition. Updated September 2019. Available at <https://www.nationalmssociety.org> (accessed January 25, 2023).
2. FDA – Label OCREVUS (ocrelizumab). Food and Drug Administration – Center for Devices and Radiologic Health (2017). Available at <https://www.accessdata.fda.gov> (accessed May 5, 2017).
3. National Institute of Neurological Disorders and Stroke (NINDS). Multiple Sclerosis: Hope through research. Available at <https://www.ninds.nih.gov> (accessed January 25, 2023).
4. FDA – Label OCREVUS (ocrelizumab). Food and Drug Administration. (Revised July 2019). Available at <https://www.accessdata.fda.gov> (accessed February 16, 2021).
5. FDA – Label OCREVUS (ocrelizumab). Food and Drug Administration. (Revised June 2024). Available at <https://www.accessdata.fda.gov> (accessed September 19, 2024).
6. FDA – Label OCREVUS ZUNOVO (ocrelizumab and hyaluronidase-ocsq). Food and Drug Administration. (Revised September 2024). Available at <https://www.accessdata.fda.gov> (accessed September 19, 2024).
7. Ocrevus Zunovo FDA Approval History. FDA Approves Ocrevus Zunovo (ocrelizumab & hyaluronidase-ocsq) Twice-A-Year Subcutaneous Injection for People With Relapsing and Progressive Multiple Sclerosis. September 17, 2024. Available at <https://www.drugs.com> (accessed September 19, 2024).
8. Newsome S, Krzystanek E, Selmaj K, et al. OCARINA II, Phase II Study: Results of Subcutaneous Ocrelizumab Administration in Patients with Multiple Sclerosis. Neurology. Apr 09 2024; 102(17 supple 1).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
11/15/2024	Document updated with literature review. The following change was made to Coverage: Added ocrelizumab and hyaluronidase-ocsq (Ocrevus Zunovo™). Added new references 6-8. Title changed from Ocrelizumab.
03/15/2024	Reviewed. No changes.
03/15/2023	Document updated with literature review. Coverage unchanged. Reference 5 was added; some references were updated, and two references were removed.

05/15/2022	Reviewed. No changes.
04/01/2021	Document updated with literature review. Coverage unchanged. References 5 and 6 added.
08/15/2020	Document updated with literature review. The following changes were made in the Coverage: 1) Relapsing forms of multiple sclerosis (MS) was clarified to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease; 2) Information regarding all immunizations was changed from 6 to 4 weeks. Reference 4 added, others updated and three were removed. Title changed from: Ocrelizumab (Ocrevus).
02/15/2019	Reviewed. No changes.
10/01/2017	New medical document. Ocrelizumab (Ocrevus®) may be considered medically necessary for the treatment of adult patients with 1) Relapsing Multiple Sclerosis (RMS) or 2) Primary Progressive Multiple Sclerosis (PPMS), AND when meeting ALL of the following criteria: hepatitis B virus (HBV) screening demonstrating that the patient is negative for active Hepatitis B virus (HBV), absence of active infection, not used in combination with another MS disease modifying agent, and not given concurrently with live vaccines. Administer all immunizations according to immunization guidelines at least 6 weeks prior to initiation of treatment. Ocrelizumab (Ocrevus) is considered experimental, investigational and/or unproven for all other indications.