Policy Number	**RX501.085**
Policy Effective Date	**5/7/2026**

Ocrelizumab or Ocrelizumab and Hyaluronidase-ocsq

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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 generally accepted standards of care developed by: nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. 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 generally accepted standards of medical care. 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 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, New England Journal of Medicine, 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 to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, or
- Primary progressive multiple sclerosis, **AND**

When meeting ALL of the following criteria:

- Hepatitis B virus 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 non-Food and Drug Administration approved indications.

Policy Guidelines

None.

Description

Ocrelizumab (Ocrevus®) is a recombinant humanized monoclonal antibody designed to target CD20 B-cell surface antigens. The precise mechanism by which ocrelizumab exerts its therapeutic effects in multiple sclerosis 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 (4)
Multiple sclerosis is the most common disabling neurological disease of young adults with symptom onset generally occurring between the ages of 20 to 40 years.

Multiple sclerosis is a chronic disease that affects people differently. A small number of those with MS will have a mild course with little to no disability, whereas others will have a steadily worsening disease that leads to increased disability over time. The natural course of MS is different for each person, which makes it difficult to predict. The onset and duration of MS symptoms usually depends on the specific type but may begin over a few days and go away quickly or develop more slowly and gradually over many years.

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.

Multiple sclerosis disease courses and their descriptions include the following (5):

- Clinically isolated syndrome - is described as a first episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation and demyelination in one or more sites in the central nervous system.

- Relapsing-remitting MS – 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 – includes steadily worsening neurologic function (accumulation of disability) from the onset of symptoms without initial relapses of remission. PPMS can be further characterized as active (showing evidence of new relapses, new gadolinium-enhancing lesions and/or new or enlarging lesions on MRI over a specified time) or not active (showing no evidence of disease activity).
- Secondary progressive MS – is 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 (Ocrevus®) received Food and Drug Administration (FDA) approval as a therapy for individuals with primary progressive and relapsing forms of multiple sclerosis. (1)

In July 2019, ocrelizumab (Ocrevus®) labeled 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. (3)

On September 13, 2024, the FDA approved Ocrevus Zunovo™ (ocrelizumab and hyaluronidase-ocsq) for individuals with primary progressive and relapsing forms of multiple sclerosis. (2) 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.

Rationale

This policy is based on the U.S. Food and Drug Administration approved labeled indications for ocrelizumab and ocrelizumab and hyaluronidase-ocsq.

Ocrelizumab (Ocrevus®) (1)
Relapsing Forms of Multiple Sclerosis
The FDA approval of ocrelizumab for relapsing multiple sclerosis was based on two randomized, double-blind, double-dummy, active comparator-controlled clinical trials of identical design, 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 score from 0 to 5.5. Patients with primary progressive forms of multiple sclerosis 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. 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.

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).

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. Results for Study 1 and Study 2 are presented in Table 1 and Figure 1.

Table 1. Key Clinical and MRI Endpoints in RMS Patients from Study 1 and Study 2

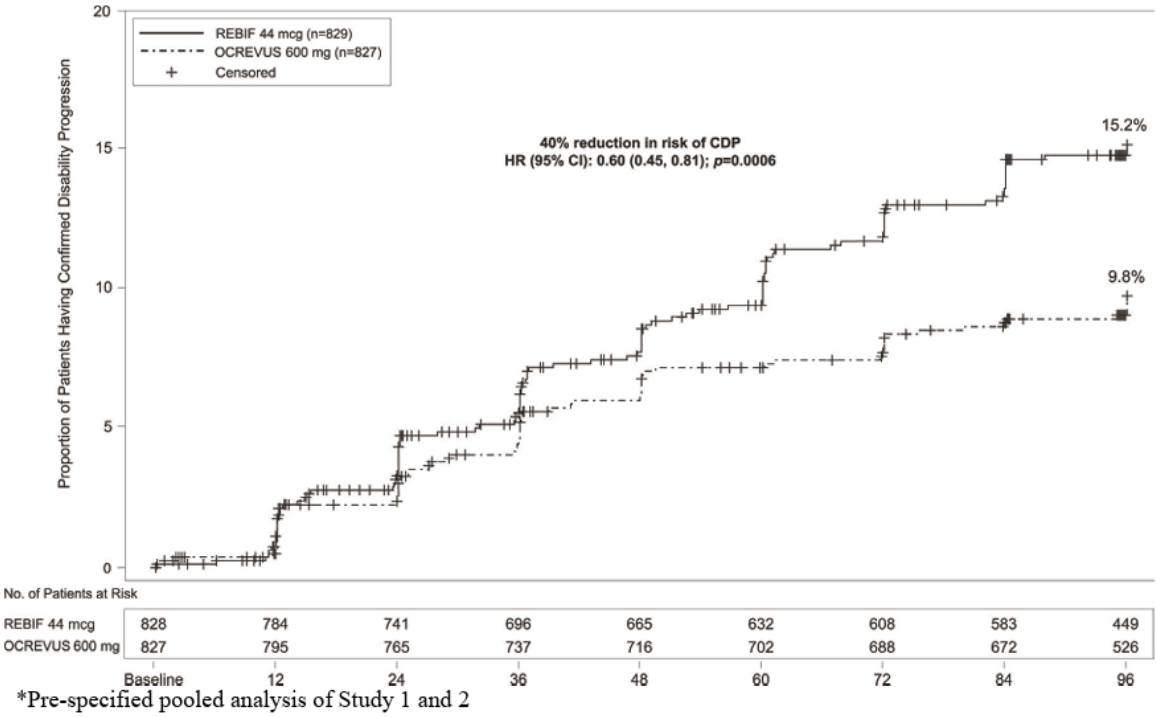
Endpoints	**Study 1**		**Study 2**	
	OCREVUS 600 mg every 24 weeks N=410	REBIF 44 mcg three times a week N=411	OCREVUS 600 mg every 24 weeks N=417	REBIF 44 mcg three times a week N=418
Clinical Endpoints				
Annualized Relapse Rate (Primary Endpoint)	0.156	0.292	0.155	0.290
Relative Reduction	46% (p<0.0001)		47% (p<0.0001)	
Proportion Relapse-free	83%	71%	82%	72%
Proportion of Patients with 12-week Confirmed Disability Progression[1]	9.8% OCREVUS vs 15.2% REBIF			
Risk Reduction (Pooled Analysis[2])	40%; p=0.0006			
MRI Endpoints				
Mean number of T1 Gd-enhancing lesions per MRI	0.016	0.286	0.021	0.416
Relative Reduction	94% (p<0.0001)		95% (p<0.0001)	
Mean number of new and/or enlarging T2 hyperintense lesions per MRI	0.323	1.413	0.325	1.904
Relative Reduction	77% (p<0.0001)		83% (p<0.0001)	

Mcg: microgram; mg: milligram; MRI: magnetic resonance imaging; RMS: relapsing forms of multiple sclerosis.

[1]Defined as an increase of 1.0 point or more from the baseline Expanded Disability Status Scale (EDSS) score for patients with baseline score of 5.5 or less, or 0.5 or more when the baseline score is greater than 5.5, Kaplan-Meier estimates at Week 96.

[2]Data prospectively pooled from Study 1 and Study 2.

Figure 1. Kaplan-Meier Plot* of Time to Onset of Confirmed Disability Progression Sustained for at Least 12 Weeks with the Initial Event of Neurological Worsening Occurring During the Double-blind Treatment Period in Pooled Studies 1 and 2 in Patients with RMS (Pooled ITT [intent to treat] Population)



*Pre-specified pooled analysis of Study 1 and 2

In exploratory subgroup analyses of Study 1 and Study 2, the effect of Ocrevus on annualized relapse rate and disability progression was similar in male and female patients.

Primary Progressive Multiple Sclerosis

Study 3 was a randomized, double-blind, placebo-controlled 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.

In Study 3, 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.

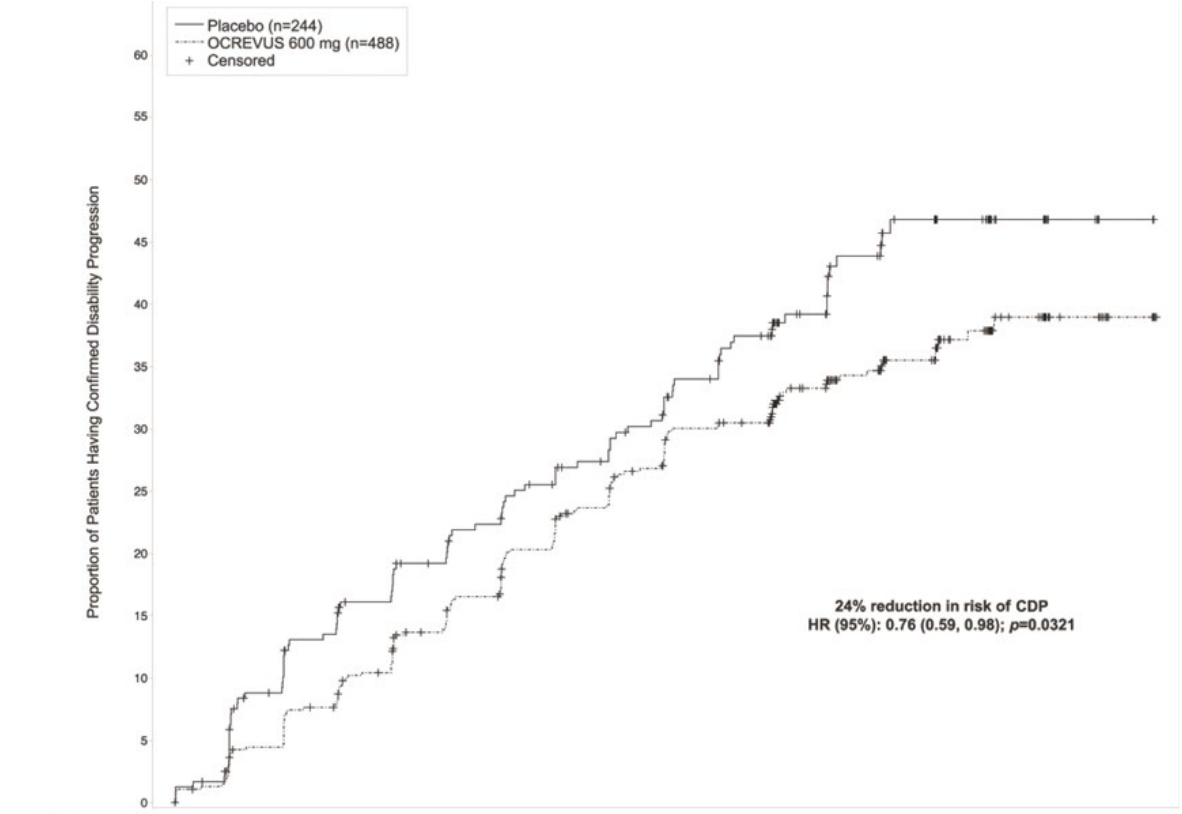
Study 3 randomized 488 patients to Ocrevus and 244 to placebo; 21% of Ocrevus-treated patients and 34% of placebo-treated patients did not complete the trial. The baseline demographic and disease characteristics were balanced between the two treatment groups. At baseline, the mean age of patients was 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. (see Figure 2). Results for Study 3 are presented in Table 2 and Figure 2.

Table 2. Key Clinical and MRI Endpoints in PPMS Patients for Study 3

Endpoints	**Study 3**	
	OCREVUS 600 mg (two 300 mg infusions two weeks apart every 24 weeks) N=488	Placebo N=244
Clinical Outcomes		
Proportion of patients with 12-week Confirmed Disability Progression[1]	32.9%	39.3%
Risk reduction	24%; p=0.0321	
MRI Endpoints		
Mean change in volume of T2 lesions, from baseline to Week 120 (cm^3)	-0.39	0.79
	p<0.0001	

MRI: magnetic resonance imaging; PPMS: primary progressive multiple sclerosis.
[1]Defined as an increase of 1.0 point or more from the baseline EDSS score for patients with baseline score of 5.5 or less, or an increase of 0.5 or more when the baseline score is more than 5.5

Figure 2. Kaplan-Meier Plot of Time to Onset of Confirmed Disability Progression Sustained for at Least 12 Weeks with the Initial Event of Neurological Worsening Occurring During the Double-blind Treatment Period in Study 3*



No. of Patients at Risk

	Baseline	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192	204	216
Placebo	244	232	212	199	189	180	172	162	153	145	136	120	85	66	46	30	20	7	2
OCREVUS 600 mg	487	462	450	431	414	391	376	355	338	319	304	281	207	166	136	80	47	20	7

*All patients in this analysis had a minimum of 120 weeks of follow-up. The primary analysis is based on all disability progression events accrued including 21 without confirmatory EDSS at 12 weeks.

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).

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.

Safety Study of 2-Hour Infusions

The safety of the 2-hour Ocrevus infusion was evaluated in Study 4 (NCT03085810), a prospective, multicenter, randomized, double-blind, controlled, parallel arm substudy in patients with Relapsing-Remitting Multiple Sclerosis who were naïve to other non-steroid therapies for MS and did not experience a serious infusion reaction with any previous OCREVUS infusion. The first dose of OCREVUS was administered as two 300 mg infusions (600 mg total) separated by 14 days. After enrollment in the substudy, patients were randomized in a 1:1 ratio to receive infusions over approximately 3.5-hours or 2-hours, after appropriate premedication [see Dosage and Administration (2.2)], every 24 weeks. The randomization was stratified by region and the dose at which patients were first randomized.

The primary endpoint of the substudy was the proportion of patients with infusion reactions occurring during or within 24 hours following the first randomized infusion of Ocrevus. The primary analysis was performed when 580 patients were randomized, at which time 469/579 (81%) of the treated patients had received only a single randomized infusion of Ocrevus. The proportions of patients with infusion reactions occurring during or within 24 hours following the first randomized infusion in this substudy were similar between the 2-hour and 3.5-hour infusion groups (24.4% versus 23.3%, respectively). Overall, in all randomized doses, 27.1% of the patients in the 2-hour infusion group and 25.0% of the patients in the 3.5-hour infusion group reported mild or moderate infusion reactions; two infusion reactions were severe in intensity, with one severe infusion reaction (0.3%) reported in one patient in each group in this substudy. There were no life-threatening, fatal, or serious infusion reactions in this substudy.

Ocrelizumab and hyaluronidase-ocsq (Ocrevus Zunovo™) (2)

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.

Ocrevus Zunovo in Patients With RMS or PPMS

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.

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, J2351

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Label:

1. FDA – Label Ocrevus (ocrelizumab). Food and Drug Administration – Food and Drug Administration. (August 2025). Available at accessdata.fda.gov (accessed January 15, 2026).
2. FDA – Label Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq). Food and Drug Administration. (August 2025). Available at accessdata.fda.gov (accessed January 15, 2026).

Other:

3. Drugs.com Ocrevus (ocrelizumab) FDA Approval History. Available at drugs.com (accessed January 15, 2026).
4. National Institute of Neurological Disorders and Stroke. Multiple Sclerosis: Hope through research. (August 1, 2020). Available at ninds.nih.gov (accessed January 15, 2026).
5. 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 nationalmssociety.org (accessed January 15, 2026).

Centers for Medicare and Medicaid Services

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 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 cms.hhs.gov.

Policy History/Revision

Date	Description of Change
5/7/2026	New medical document. 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 to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, or Primary progressive multiple sclerosis, 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 non-Food and Drug Administration approved indications.