Medical Drug Clinical Criteria

Subject:	Ocrevus (ocrelizumab)/Ocrevus Zunovo (ocrelizumab/hyaluronidase-ocsq)		
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Overview

This document addresses the use of Ocrevus (ocrelizumab) and Ocrevus Zunovo (ocrelizumab/hyaluronidase-ocsq), disease modifying therapies approved by the Food and Drug Administration (FDA) to treat primary progressive multiple sclerosis in adults and relapsing multiple sclerosis in adults, including clinically isolated syndrome, relapsing-remitting disease and active secondary progressive disease. Ocrevus is administered via intravenous infusion, and Ocrevus Zunovo is administered via subcutaneous infusion.

Multiple sclerosis is an autoimmune inflammatory demyelinating disease of the central nervous system. Common symptoms of the disease include fatigue, numbness, coordination and balance problems, bowel and bladder dysfunction, emotional and cognitive changes, spasticity, vision problems, dizziness, sexual dysfunction and pain. Multiple sclerosis can be subdivided into four phenotypes: clinically isolated syndrome (CIS), relapsing remitting (RRMS), primary progressive (PPMS) and secondary progressive (SPMS). Relapsing multiple sclerosis (RMS) is a general term for all relapsing forms of multiple sclerosis including CIS, RRMS and active SPMS.

The treatment goal for multiple sclerosis is to prevent relapses and progressive worsening of the disease. Currently available disease-modifying therapies (DMT) are most effective for the relapsing-remitting form of multiple sclerosis and less effective for secondary progressive decline. DMT include injectable agents, infusion therapies and oral agents.

The FDA approval of Ocrevus for relapsing multiple sclerosis (RMS) was based on two identically designed Phase III double-blind, double-dummy randomized controlled trials, OPERA I and II. Approval for primary progressive multiple sclerosis (PPMS) was based on a randomized, double-blind, placebo-control Phase III clinical trial, ORATORIO.

In the OPERA I and II trials, 1656 study participants were randomized 1:1 to receive Ocrevus or interferon beta-1a (IFN β -1a). Notable inclusion criteria included diagnosis of multiple sclerosis according to the revised McDonald criteria, at least two documented clinical attacks within the last two years prior to screening or one clinical attack in the year prior to screening, neurologic stability for at least the past 30 days at baseline and expanded disability status scale (EDSS) score of 0-5.5. Exclusion criteria included diagnosed with PPMS, EDSS score of < 2.1 with a disease duration over 10 years, immunosuppression and active infection. The primary endpoint in the studies was the annualized relapse rate at week 96 (2 years). Secondary endpoints included confirmed disability progression (CDP) at weeks 12 and 24 and the number of new or enhancing T1 and T2 lesions as seen on MRI at weeks 24, 48 and 96. The superior efficacy of Ocrevus in reducing the annualized relapse rate and disability progression was demonstrated and sustained compared to standard of care IFN β -1a at week 96. In both OPERA I and II, the annualized relapse rate was 16% compared to 29% in the subjects treated with IFN β -1a (absolute risk reduction 13%, NNT = 8, 46% relative risk reduction; p<0.001). The secondary endpoint of a reduction in CDP was also met at week 24 (Hazard Ratio [HR]=0.60, p=0.003). Additionally, the secondary endpoints of a reduction in T1 Gd+ lesions and new/enlarging T2 lesions were also significantly reduced in Ocrevus arms (p<0.0001). There was no significant difference detected in the quality of life between the two arms. Overall, in OPERA I and OPERA II, Ocrevus had a similar safety profile compared with IFN β-1a over 96 weeks.

ORATORIO evaluated the efficacy and safety of Ocrevus (n=488) compared to placebo (n=244) in 732 individuals diagnosed with PPMS who were randomized 2:1. The primary outcome of interest was time to onset of sustained disability progression, defined as an increase in EDSS score that is sustained for at least 12 weeks. Secondary outcomes included interim analysis of the primary outcome at 24 weeks, change in 25-foot walk test from baseline to 120 weeks, and change in volume of T2 brain lesions on MRI. Inclusion criteria included a diagnosis of PPMS as defined by the McDonald criteria and EDSS score of 3 to 6.5. Those with a history of relapsing forms of MS or secondary progressive MS (SPMS) were excluded as were those with other neurologic disorders, active infection, previous treatment with B-cell targeted therapies or lymphocyte trafficking blockers and comorbidities that may require chronic immunosuppressive therapy. The study's primary endpoint was met. A total of 32.9% of subjects in the Ocrevus arm experienced disability progression lasting 12 weeks or longer compared to 39.3% of subjects in the placebo arm (absolute risk reduction, 6.4%; NNT = 16; HR=0.76, 95% Confidence Interval [CI], 0.59-0.98; p=0.03). A total of 29.6% of Ocrevus subjects experienced disability lasting 24 weeks or longer compared to 35.7% of the subjects receiving placebo injections (absolute risk reduction 6.1%, NNT=17, HR=0.75, 95%

CI, 0.58-0.98; p=0.04). At week 120, 402 individuals (82%) in the Ocrevus group and 174 individuals (71%) in the placebo group were available for analysis. There was a statistically significant reduction in the progression rate of 25-foot walk time from baseline to week 120 (55.1% change from baseline in placebo and 38.9% change from baseline in the Ocrevus arm, absolute risk reduction 16.2%, relative risk reduction=29.3% [95% CI, -1.6 to 51.5), p=0.04). The secondary endpoints of reduction in T2 brain lesion volume (mean percent change -3.4 vs +7.4; p<0.0001) as well as the rate of whole brain volume loss (-0.90 vs. -1.09; p=0.02) also favored Ocrevus over placebo at week 120. The mean treatment duration was approximately 3 years, during which time the proportion of study participants experiencing AEs and serious AEs associated with Ocrevus, was similar to placebo. The most serious events were mild-to-moderate infusion-related reactions. A notable potential safety concern was that 2.3% of the Ocrevus arm (n=11; 4 breast cancer, 3 basal cell carcinoma, and 1 each of endometrial adenocarcinoma, anaplastic large cell lymphoma, malignant fibrous histiocytoma, and pancreatic carcinoma) were diagnosed with a malignant neoplasm while only 0.8% (n=2) of the placebo arm were diagnosed with a malignant neoplasm.

The American Academy of Neurology (AAN) guidelines suggest starting disease-modifying therapy in individuals with relapsing forms of multiple sclerosis with recent clinical relapses or MRI activity. The guidelines also suggest DMT for individuals who have experienced a single clinical demyelinating event and two or more brain lesions consistent with multiple sclerosis if the individual wishes to start therapy after a risks and benefits discussion. The guidelines do not recommend one DMT over another. The AAN guidelines also state Ocrevus is the only DMT shown to alter disease progression in individuals with primary progressive multiple sclerosis who are ambulatory and provides a recommendation for Ocrevus for this population.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Ocrevus (ocrelizumab)/Ocrevus Zunovo (ocrelizumab/hyaluronidase-ocsq)

Requests for Ocrevus (ocrelizumab) and Ocrevus Zunovo (ocrelizumab/hyaluronidase-ocsq) may be approved if the following criteria are met:

I. Individual has a diagnosis of primary progressive multiple sclerosis (PPMS); **AND**
II. Individual is able to ambulate more than 5 meters (not considered wheelchair bound);
OR
III. Individual has a diagnosis of relapsing multiple sclerosis (RMS) (including clinically isolated syndrome, relapsing-remitting disease or active secondary progressive disease); **AND**
IV. Individual is able to ambulate without aid or rest for at least 100 meters; **AND**
V. If initiating therapy, individual has experienced at least two relapses within the previous two years or one relapse within the previous year.

Ocrevus (ocrelizumab) and Ocrevus Zunovo (ocrelizumab/hyaluronidase-ocsq) may not be approved for the following:

I. Individual has active hepatitis B or hepatitis C virus infection or another active infection at initiation of therapy; **OR**
II. Individual has a history of life-threatening infusion reaction to Ocrevus/Ocrevus Zunovo; **OR**
III. Individual is using to treat non-active secondary progressive multiple sclerosis; **OR**
IV. Individual is using to treat systemic lupus erythematosus; **OR**
V. Individual is using to treat rheumatoid arthritis; **OR**
VI. Use in combination with other MS disease modifying agents (including Aubagio, Avonex, Bafiertam, Betaseron, Briumvi, Copaxone/Glatiramer/Glatopa, Extavia, Gilenya, Kesimpta, Lemtrada, Mavenclad, Mayzent, Plegridy, Ponvory, Rebif, Tascenso ODT, Tecfidera, Tyruko, Tysabri, Vumerity and Zeposia); **OR**
VII. May not be approved when the above criteria are not met and for all other indications.

Quantity Limits

Ocrevus (ocrelizumab)/ Ocrevus Zunovo (ocrelizumab/hyaluronidase-ocsq) Quantity Limit

Drug	Limit
Ocrevus (ocrelizumab) 300 mg/10 mL single dose vial	2 vials per 6 months
Ocrevus Zunovo (ocrelizumab/hyaluronidase-ocsq) 920 mg and 23,000 units/23 mL single-dose vial	1 vial per 6 months

Step Therapy

Note: When Ocrevus (ocrelizumab) is deemed approvable based on the clinical criteria referenced above, the benefit plan may have additional criteria requiring the use of a preferred[1] agent or agents.

Ocrevus/Ocrevus Zunovo Step Therapy

A benefit plan may select any one or more of the following as preferred for multiple sclerosis: fumaric acid derivatives: monomethyl fumarate (Bafiertam), Tecfidera, dimethyl fumarate, diroximel fumarate (Vumerity). A list of the preferred products is available here.

Commercial
Requests for Ocrevus (ocrelizumab) or Ocrevus Zunovo may be approved when the following criteria are met:

I. Documentation is provided that individual has been on Ocrevus (ocrelizumab) or Ocrevus Zunovo;

OR

II. Documentation has been provided that individual has had a trial and inadequate response (including but not limited to clinical relapse, new or enlarged lesions on MRI or confirmed disability progression) or intolerance to the following:
   A. Preferred fumaric acid derivative;

OR

III. Documentation is provided that individual has high disease activity despite treatment with fingolimod (Gilenya, Tascenso ODT) defined as the following (AAN 2018, Devonshire 2012):
   A. At least one relapse in the previous year while on therapy; **AND**
   B. At least 9 T_2-hyperintense lesions in cranial MRI;

   OR
   C. At least one Gadolinium-enhancing lesion;

OR

IV. Documentation is provided that individual is requesting Ocrevus or Ocrevus Zunovo for the treatment of primary progressive multiple sclerosis.

Medicaid
Requests for Ocrevus (ocrelizumab) may be approved when the following criteria are met:

I. Documentation is provided that individual has been on Ocrevus (ocrelizumab);

OR

II. Documentation has been provided that individual has had a trial and inadequate response (including but not limited to clinical relapse, new or enlarged, lesions on MRI or confirmed disability progression) or intolerance to the following:
   A. Preferred fumaric acid derivative;

AND

III. Documentation has been provided that individual has had a trial and inadequate response (including but not limited to clinical relapse, new or enlarged, lesions on MRI or confirmed disability progression) or intolerance to Kesimpta;

OR

IV. Documentation is provided that individual has high disease activity despite treatment with fingolimod (Gilenya, Tascenso ODT) defined as the following (AAN 2018, Devonshire 2012):
   A. At least one relapse in the previous year while on therapy; **AND**
   B. At least 9 T_2-hyperintense lesions in cranial MRI;

   OR
   C. At least one Gadolinium-enhancing lesion;

OR

V. Documentation is provided that individual is requesting Ocrevus for the treatment of primary progressive multiple sclerosis.

[1]Preferred, as used herein, refers to agents that were deemed to be clinically comparable to other agents in the same class or disease category but are preferred based upon clinical evidence and cost effectiveness.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement

policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J2350	Injection, ocrelizumab, 1 mg [Ocrevus]
J2351	Injection, ocrelizumab, 1 mg and hyaluronidase-ocsq [Ocrevus Zunovo]

ICD-10 Diagnosis

G35	Multiple sclerosis

Document History

Revised: 11/15/2024
Document History:

- 03/04/2025 – Coding Update: Removed HCPCS NOC J3590 and added J2351 for Ocrevus Zunovo effective 4/1/25.
- 11/15/2024 – Annual Review: Add Tyruko to exclusion for concurrent use with other disease modifying therapy criteria. Step therapy table updates. Coding reviewed: No changes.
- 9/17/2024 – Select Review: Add Ocrevus Zunovo to clinical criteria and quantity limit. Coding reviewed: Added HCPCS J3590 for Ocrevus Zunovo.
- 03/01/2024 – Administrative update to add documentation.
- 11/17/2023 – Annual Review: Add Briumvi and Tascenso ODT to exclusion for concurrent use with other disease modifying therapy criteria. Coding Reviewed: No changes.
- 07/05/2023 – Step therapy table updates.
- 03/27/2023 – Step therapy table updates.
- 01/25/2023 – Step therapy language update.
- 8/19/2022 – Annual Review: Wording and formatting changes. Coding reviewed: No changes.
- 8/20/2021 – Annual Review: Update drug list in exclusion for concurrent use with other disease modifying therapy. Coding reviewed: No changes.
- 04/26/2021 – Step Therapy table update.
- 03/23/2021 – Step Therapy table update.
- 11/20/2020 – Select Review: Clarify inadequate response step therapy language. Update the preferred option to only the preferred fumaric acid derivative. Add override criteria for individuals with high disease activity despite treatment with Gilenya.
- 11/01/2020 - Administrative update to modify step therapy.
- 10/26/2020 – Administrative update to add step therapy.
- 8/21/2020 – Annual Review: Update drug list in exclusion for concurrent use with other disease modifying therapy. Coding reviewed: No changes.
- 07/20/2020 – Administrative update to add drug specific quantity limits.
- 08/16/2019 – Annual Review: Update criteria to align with updated labeled indication. Wording and formatting changes. Coding Reviewed: No changes
- 03/18/2019 – Selected Review: Wording and formatting changes. Coding Reviewed: No changes.
- 08/17/2018 – Annual Review: Initial review of ING-CC-0011 Ocrevus (ocrelizumab). Removed diagnostic confirmation and age criteria for consistency with criteria for other MS agents. Updated exclusion for active hepatitis B/C to also exclude if any other active infection is present. Added exclusion for concurrent use with another MS agent.

References

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: October 23, 2024.
2. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
3. Expanded Disability Status Scale (EDSS). Department of Veterans Affairs: Multiple Sclerosis Centers for Excellence. Last updated: March 18, 2021. Available at: https://www.va.gov/MS/Professionals/diagnosis/Kurtzke_Expanded_Disability_Status_Scale.asp. Accessed: October 27, 2024.
4. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc. Updated periodically.
5. Olek MJ, Howard J. Clinical presentation, course and prognosis of multiple sclerosis in adults. Last updated: April 26, 2024. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed: October 27, 2024.
6. 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: 777-788. Available from: https://www.aan.com/Guidelines/home/GuidelineDetail/898. Accessed: October 27, 2024.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

CC-0011 Ocrevus

Commercial

Effective Date	Preferred Agents	Non-Preferred Agents
02/01/2021	Fumaric acid derivative: generic dimethyl fumarate	Ocrevus
03/01/2025	Fumaric acid derivative: generic dimethyl fumarate	Ocrevus Ocrevus Zunovo

Medicaid

Effective Date	Preferred Agents	Non-Preferred Agents
04/01/2021: MD, NJ, NV, NY, SC, WNY 05/01/2021: GA 04/01/2023: DC	Fumaric acid derivative: generic dimethyl fumarate Kesimpta (may require step therapy)	Ocrevus

Medicare

Effective Date	Preferred Agents	Non-Preferred Agents
N/A	N/A	N/A