Original Effective Date: 08/01/2017
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Policy Number: C11250-A

Ocrevus (ocrelizumab)

PRODUCTS AFFECTED

Ocrevus (ocrelizumab), Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Multiple Sclerosis (MS)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. ALL INDICATIONS:
1. Documentation of screening for hepatitis B virus AND for patients who are negative for surface antigen [HBsAg] and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], documentation of a consult with a liver disease expert before starting treatment
AND

2. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Ocrevus (ocrelizumab) include: Active hepatitis B virus infection, history of life-threatening infusion reaction to Ocrevus.]

B. RELAPSING FORMS OF MULTIPLE SCLEROSIS:

1. Documentation of a definitive diagnosis of a relapsing form of multiple sclerosis including: Relapsing- remitting multiple sclerosis [RRMS], secondary-progressive multiple sclerosis [SPMS] with relapses, and clinically isolated syndrome
   AND
2. (a) Documentation of **inadequate response (trial of 3 months) to ONE of the following: ONE of Interferon therapy (Avonex, Rebif, Extavia, Betaseron, Plegridy) OR Glatiramer OR formulary oral disease modifying therapy [e.g., Aubagio (teriflunomide), Tecfidera (dimethyl fumarate), Gilenya (fingolimod), etc.]
   **Inadequate response is defined as meeting at least TWO of the following three criteria during treatment: 1) Clinical relapses (at least two relapses within the past 12 months), 2) CNS lesion progression as measured by MRI, OR 3) Worsening disability (e.g., sustained worsening of EDSS score or neurological exam findings; worsening disability including, but not limited to, decreased mobility, decreased ability to perform activities of daily living due to disease progression, or EDSS > 3.5)
   OR
   (b) Documentation member has indicators of a highly active course of multiple sclerosis: (i) age of MS onset $\geq$ 40 years of age, (ii) male gender, (iii) African American, (iv) motor, sphincter, brainstem-cerebellar symptoms, (v) MRI lesions in brainstem or spinal cord, OR (vi) $\geq$ 2 acute relapses in first 2 years of onset with significant sustained disability following relapse
   AND
3. IF REQUEST IS FOR A NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of trial/failure of, or serious side effects to a majority (not more than 3) of the preferred formulary/PDL alternatives for the given diagnosis. Submit documentation including medication(s) tried, dates of trial(s) and reason for **treatment failure(s).
   **May be defined as meeting at least TWO of the following three criteria during treatment:
   1) Clinical relapses (at least two relapses within the past 12 months), 2) CNS lesion progression as measured by MRI, OR 3) Worsening disability (e.g., sustained worsening of EDSS score or neurological exam findings; worsening disability including, but not limited to, decreased mobility, decreased ability to perform activities of daily living due to disease progression, or EDSS > 3.5)

C. PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS:

1. Documentation of a diagnosis of primary progressive multiple sclerosis (PPMS)

CONTINUATION OF THERAPY:

A. RELAPSING FORM OF MULTIPLE SCLEROSIS:

1. Documentation of positive clinical response or stable disease based on ONE of the following:
   (a) Documentation of a stable number or decrease in acute attacks (relapses) within the last 6 months
   OR
   (b) Documentation of lack of progression or sustained disability
   OR
   (c) Recent (within last 6 months) MRI shows lack of development of new asymptomatic lesions
   AND
2. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity (e.g., serious opportunistic or recurrent infections, etc.)

B. PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS:

1. Documentation of positive clinical response or stable disease based on ONE of the following:
   (a) Documentation of lack of progression or sustained disability
   OR
   (b) Recent (within last 6 months) MRI shows lack of development of new asymptomatic lesions
   AND
2. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity (e.g., serious opportunistic or recurrent infections, etc.)

DURATION OF APPROVAL:
Initial Authorization: 12 months, Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a board-certified neurologist or a multiple sclerosis specialist. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
IV:
Starting dose: 300mg once, followed two weeks later by a second 300mg infusion
Subsequent doses: 600mg every 6 months

SC infusion:
920 mg/23,000 units (920 mg ocrelizumab and 23,000 units of hyaluronidase) administered as a single 23 mL subcutaneous injection in the abdomen every 6 months.

PLACE OF ADMINISTRATION:
The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.

The recommendation is that injectable medications in this policy will be for pharmacy or medical benefit coverage and the subcutaneous injectable products administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.

Note: Site of Care Utilization Management Policy applies for Ocrevus (ocrelizumab) and Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq). For information on site of care, see Specialty Medication Administration Site of Care Coverage Criteria (molinamarketplace.com)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intravenous infusion and subcutaneous injection

DRUG CLASS:
Multiple Sclerosis Agents - Monoclonal Antibodies

FDA-APPROVED USES:

Drug and Biologic Coverage Criteria

Indicated for the treatment of:

- Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
- Primary progressive MS, in adults

COMPENDIAL APPROVED OFF-LABELED USES:

None

APPENDIX

APPENDIX:

Summary of 2017 McDonald Criteria for the Diagnosis of MS

CLINICAL PRESENTATION	ADDITIONAL CRITERIA TO MAKE MS DIAGNOSIS
...in a person who has experienced a typical attack/CIS at onset	
• 2 or more attacks and clinical evidence of 2 or more lesions; OR • 2 or more attacks and clinical evidence of 1 lesion with clear historical evidence of prior attack involving lesion in different location	None. DIS and DIT have been met.
• 2 or more attacks and clinical evidence of 1 lesion	DIS shown by one of these criteria: - additional clinical attack implicating different CNS site - 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxtacortical, infratentorial or spinal cord
• 1 attack and clinical evidence of 2 or more lesions	DIT shown by one of these criteria: - Additional clinical attack - Simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF oligoclonal bands
• 1 attack and clinical evidence of 1 lesion	DIS shown by one of these criteria: - Additional attack implicating different CNS site - 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxtacortical, infratentorial or spinal cord **AND** DIT shown by one of these criteria: - additional clinical attack - Simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF oligoclonal bands
...in a person who has steady progression of disease since onset	
1 year of disease progression (retrospective or prospective)	DIS shown by at least two of these criteria: - 1 or more MS-typical T2 lesions (periventricular, cortical, juxtacortical or infratentorial) - 2 or more T2 spinal cord lesions - CSF oligoclonal bands

DIT = Dissemination in time **CNS** = central nervous system **CSF** = cerebrospinal fluid
DIS = Dissemination in space **T2 lesion** = hyperintense lesion on T2-weighted MRI

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Ocrevus is a CD20-directed cytolytic antibody indicated for the treatment of patients with relapsing or primary progressive forms of multiple sclerosis (MS).1 The efficacy of Ocrevus in patients with relapsing MS was established in two identical, Phase III, multicenter, randomized, double-blind, double-dummy, active controlled, published, parallel group trials (OPERA I and OPERA II), that used Rebif® (interferon beta-1a subcutaneous [SC]) as an active comparator for up to 96 weeks.2 Approximately 25% of patients had previously used MS disease-modifying therapy (mainly beta interferon or glatiramer acetate products). In these two trials (OPERA I n = 821 and OPERA II n =825) the annualized relapse rate (ARR) among patients with relapsing MS was lower with Ocrevus in both studies compared with Rebif (0.16 vs. 0.29; P < 0.001). In a prespecified analysis the percentage of patients with disability progression confirmed at 12 weeks was significantly lower with Ocrevus compared with Rebif (9.1% vs. 13.6%; P < 0.001), as well as the percentage of patients with disability progression confirmed at 24 weeks (6.9% vs. 10.5%; P = 0.001). Several magnetic resonance imaging (MRI) parameters were also more favorable with Ocrevus vs. Rebif. The percentage of patients with no evidence of disease activity by Week 96, an exploratory endpoint, was also statistically significantly larger for patients given Ocrevus vs. Rebif (47.9% vs. 29.2%; P < 0.001). The efficacy of Ocrevus in patients with primary progressive MS was established in one Phase III, randomized, parallel-group, double-blind, placebo-controlled published trial (ORATORIO

[n = 732]).3 Therapy duration was at least 120 weeks. Most patients (88%) had not previously used MS disease-modifying therapy. In ORATORIO the primary endpoint was the percentage of patients with disability progression confirmed as 12 weeks in a time-to-event analysis that defined disability progression as an increase in the Expanded Disability Status Scale (EDSS) of at least 1.0 point from baseline that was sustained on subsequent visits for at least 12 weeks if the baseline score was 5.5 or less or an increase of at least 0.5 points that was sustained for at least 12 weeks if the baseline EDSS score was more than 5.5.

The percentage of patients with primary progressive MS with 12-week confirmed disability progression was 32.9% with Ocrevus vs. 39.3% with placebo (P = 0.03). The percentage of patients with 24-week confirmed disability progression was 29.6% with Ocrevus vs. 35.7% with placebo (P = 0.04). By Week 120, performance on the timed 25-foot walk worsened by 38.9% with Ocrevus vs. 55.1% with placebo (P = 0.04). More favorable MRI results on several parameters were also observed with Ocrevus compared with placebo.

Progressive Multifocal Leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients with MS treated with OCREVUS in the postmarketing setting. PML is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. PML has occurred in OCREVUS-treated patients who had not been treated previously with natalizumab (which has a known association with PML), were not taking any immunosuppressive or immunomodulatory medications associated with the risk of PML prior to or concomitantly with OCREVUS, and did not have any known ongoing systemic medical conditions resulting in compromised immune system function. JCV infection resulting in PML has also been observed in patients treated with other anti-CD20 antibodies and other MS therapies. At the first sign or symptom suggestive of PML, withhold OCREVUS and perform an appropriate diagnostic evaluation. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. MRI findings may be apparent before clinical signs or symptoms. Cases of PML, diagnosed based on MRI findings and the detection of JCV DNA in the cerebrospinal fluid in the absence of clinical signs or symptoms specific to PML, have been reported in patients treated with other MS medications associated with PML. Many of these patients subsequently became symptomatic with PML. Therefore, monitoring with MRI for signs that may be consistent with PML may be useful, and any suspicious findings should lead to further investigation to allow for an early diagnosis of PML, if present. Following discontinuation of another MS medication associated with PML, lower PML-related mortality and morbidity have been reported in patients who were initially asymptomatic at diagnosis compared to patients who had characteristic clinical signs and symptoms at diagnosis. It is not known whether these differences are due to early detection and discontinuation of MS treatment or due to differences in disease in these patients. If PML is confirmed, treatment with OCREVUS should be discontinued.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Ocrevus (ocrelizumab) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications to Ocrevus (ocrelizumab) include: active hepatitis B virus (HBV) infection, and history of life-threatening infusion reaction to Ocrevus.

Exclusions/Discontinuation:

Based on animal data, ocrelizumab may cause fetal harm when administered to a pregnant woman. Prior to initiating ocrelizumab, perform testing for quantitative serum immunoglobulins. For patients with low serum immunoglobulins, consult immunology experts before initiating treatment with ocrelizumab. Monitor the levels of quantitative serum immunoglobulins during treatment and after discontinuation of treatment, until B-cell repletion, and especially in the setting of recurrent serious infections. Consider discontinuing ocrelizumab therapy in patients with serious opportunistic or recurrent serious infections, and

if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.
Because vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation until B-cell repletion, administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of ocrelizumab for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of ocrelizumab for non-live vaccines.
Member is not currently being treated with a disease modifying agent (DMA) other than the requested agent, B cell targeted therapy (e.g., rituximab, belimumab, ofatumumab), or lymphocyte trafficking blocker (e.g., alemtuzumab, mitoxantrone).

OTHER SPECIAL CONSIDERATIONS:
If a planned infusion of Ocrevus is missed, administer Ocrevus as soon as possible; do not wait until the next scheduled dose. Reset the dose schedule to administer the next sequential dose 6 months after the missed dose is administered. Doses of Ocrevus must be separated by at least 5 months

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
J2350	Injection, ocrelizumab,1mg
J2351	Injection, ocrelizumab, 1 mg and hyaluronidase-ocsq

AVAILABLE DOSAGE FORMS:
Ocrevus SOLN 300MG/10ML single dose vial
Ocrevus Zunovo SOLN 920-23000MG-UT/23ML single-dose vial

REFERENCES

1. Ocrevus (ocrelizumab) injection, for intravenous infusion [prescribing information]. San Francisco, CA: Genentech, Inc; June 2024.
2. Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) injection, for subcutaneous use) [prescribing information]. South San Francisco, CA: Genentech Inc; September 2024.
3. Hauser SL, Bar-Or A, Comig G, et al, for the OPERA I and OPERA II Clinical Investigators. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med. 2016 Dec 21. [Epub ahead of print].
4. Montalban X, Hauser SL, Kappos L, et al, for the ORATORIO Clinical Investigators. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med. 2016 Dec 21. [Epub ahead of print].
5. Clinical bulletin. Information for health professionals. Overview of multiple sclerosis. Rosalind Kalb and Nancy Reitman. © 2012 National Multiple Sclerosis Society. Available at: http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/C li ni cal_Bulletin_Overview-ofMultiple-Sclerosis.pdf. Accessed on March 7, 2017.

6. Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis: principles and current evidence. July 2014. Available at: Accessed on March 7, 2017.
7. Gajofatto A, Turatti M, Benedetti MD. Primary progressive multiple sclerosis: current therapeutic strategies and future perspectives. Expert Rev Neurother. 2016 Nov 15:1- 14. [Epub ahead of print]
8. 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 [published correction appears in Neurology. 2019;92(2):112]. Neurology. 2018;90(17):777-788. doi: 10.1212/WNL.0000000000005347. [PubMed 29686116]
9. Thompson, A., Banwell, B., et al. (2018). Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The Lancet Neurology, 17(2), pp.162-173

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Place of Administration Contraindications/Exclusions/Discontinuation References	Q2 2025
REVISION- Notable revisions: Continuation of Therapy	Q1 2025
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Other Special Considerations References	Q2 2024
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements Quantity Background Contraindications/Exclusions/Discontinuation Available Dosage Forms References	Q2 2023
REVISION- Notable revisions: Duration of Approval References	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file