Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Ocrelizumab [Ocrevus®], Ocrelizumab/hyaluronidase-ocsq [Ocrevus Zunovo®]	MP-RX-FP-64-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B DRUG

Service Description

This document addresses the use of *ocrelizumab (Ocrevus®) and ocrelizumab/hyaluronidase-ocsq [Ocrevus Zunovo®],* an infused disease modifying therapy 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.

Background Information

Mechanism of Action: 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.

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.

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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% 2 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,

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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.

Approved Indications (FDA Label indications)

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

B. Primary progressive MS, in adults.

Other Uses (off-label uses, example: NCCN)

i. N/A

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J2350	Injection, ocrelizumab, 1 mg [Ocrevus®]
J3590	Unclassified biologics [Ocrevus Zunovo®]

ICD-10	Description
G35	Multiple sclerosis

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Medical Necessity Guidelines

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.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Clinical Criteria

Ocrelizumab (Ocrevus®) and Ocrelizumab/hyaluronidase (Ocrevus Zunovo®)

A. Criteria for Initial Approval

Initial requests for ocrelizumab (Ocrevus) and ocrelizumab/hyaluronidase-ocsq (Ocrevus Zunovo) 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.

B. Criteria for Continuation Therapy

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

i. Progress notes or clinical documentation from the prescriber confirms that the patient requires continued treatment and has demonstrated stabilization and/or improvement in disease activity; **AND**
ii. There is no evidence of treatment-limiting adverse effects with ocrelizumab.

C. Conditions not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

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

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A. Individual has active hepatitis B or hepatitis C virus infection or another active infection at initiation of therapy; **OR**
B. Individual has a history of life-threatening infusion reaction to Ocrevus; **OR**
C. Individual is using to treat non-active secondary progressive multiple sclerosis; **OR**
D. Individual is using to treat systemic lupus erythematosus; **OR**
E. Individual is using to treat rheumatoid arthritis; **OR**
F. 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, Tysabri, Vumerity and Zeposia); **OR**
G. May not be approved when the above criteria are not met and for all other indications

D. Authorization Duration

i. Initial Approval Duration: Up to 12 months
ii. Reauthorization Approval Duration: Up to 12 months

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Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Ocrelizumab (Ocrevus®) and Ocrelizumab/hyaluronidase (Ocrevus Zunovo®)

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
Exceptions	
None	

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Reference Information

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: July 7, 2022.
2. Devonshire V, Havrdova E, Radue EW, et al. Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. Lancet Neurol. 2012; 11:420-28. DOI: http://dx.doi.org/10.1016/S1474-4422(12)70056-X.
3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc. Updated periodically.
5. 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: January 4, 2023.

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.

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Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review 9/27/2024	Add: approved indications, other uses, conditions not covered, Approval duration, therapeutic alternatives and federal statement. Add Ocrevus Zunovo to policy and document name, clinical criteria and quantity limit. Wording and formatting changes. Coding reviewed: Added HCPCS J3590 for Ocrevus Zunovo.	2/24/2025	3/6/2025
Select Review	Removal of step therapy requirement	4/18/2024	6/28/2024
Policy Inception 9/27/2023	Elevance Health's Medical Policy adoption.	N/A	11/30/2023

Revised: 9/27/24