

Corporate Medical Policy

Ocrelizumab (Ocrevus[®])

File Name:	ocrelizumab (ocrevus)
Origination:	6/2017
Last CAP Review:	5/2020
Next CAP Review:	5/2021
Last Review:	8/2020

Description of Procedure or Service

Ocrelizumab (Ocrevus[®]) is a CD20- directed cytologic antibody indicated for the treatment of patients with relapsing or primary progressive forms of multiple sclerosis.

REGULATORY STATUS

On March 28, 2017, the U.S. Food and Drug Administration (FDA) approved Ocrevus (ocrelizumab) for treatment of adult patients with relapsing or primary progressive forms of multiple sclerosis. This represents the first product approved for primary progressive multiple sclerosis.

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for Ocrelizumab (Ocrevus) when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Ocrelizumab (Ocrevus) is covered

Ocrelizumab is considered medically necessary for the treatment of relapsing forms of multiple sclerosis (to include clinically isolated syndrome, relapsing-remitting disease and active secondary progressive disease) or primary progressive forms of multiple sclerosis in adult individuals who meet both of the following criteria:

1. The patient must be able to stand and ambulate at least a few steps, with or without aid; or alternatively must have some functional arm/ hand use consistent with ability to perform activities of daily living; AND
2. The patient is not receiving 2 or more disease modifying drugs for multiple sclerosis.

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When Ocrelizumab (Ocrevus) is not covered

Use of ocrelizumab is considered investigational when the criteria above are not met, and for all other indications.

Policy Guidelines

Prior to initiating Ocrevus, Hepatitis B virus (HBV) screening should be performed. Ocrevus is contraindicated in patients with active HBV confirmed by positive results for HBsAg and anti-HBV tests. For patients who are negative for surface antigen [HBsAg] and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], consult liver disease experts before and starting and during treatment.

Vaccination with live-attenuated or live vaccines is not recommended during Ocrevus treatment and after discontinuation until B-cell repletion; thus, all immunizations should be administered according to immunization guidelines at least 4 weeks prior to initiating Ocrevus for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiating Ocrevus for non-live vaccines. Ocrevus may interfere with the effectiveness of non-live vaccines.

Ocrevus can cause infusion reactions, which can include pruritus, rash, urticaria, erythema, bronchospasm, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, fever, fatigue, headache, dizziness, nausea, tachycardia, and anaphylaxis. Patients treated with Ocrevus should be observed for infusion-related reactions during the infusion and for at least one hour after completion of the infusion. Ocrevus should be permanently discontinued should a life-threatening or disabling infusion reaction occur.

Relapsing Forms of Multiple Sclerosis (RMS)

The efficacy of Ocrevus was demonstrated in 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 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 MRIs 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.

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

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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.

Primary Progressive Multiple Sclerosis (PPMS)

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.

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.

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Ocrelizumab Site of Care Eligibility

1. Ocrelizumab administration may be given in an inpatient setting if the inpatient setting is medically necessary. An inpatient admission for the sole purpose of ocrelizumab infusion is not medically necessary, OR
2. Ocrelizumab administration in a hospital outpatient setting is considered medically necessary if the following criteria are met:
 - a. History of mild adverse events that have not been successfully managed through mild pre-medication (diphenhydramine, acetaminophen, steroids, fluids, etc.), OR
 - b. Inability to physically and cognitively adhere to the treatment schedule and regimen complexity, OR
 - c. One of the following:
 - a. The patient is new to therapy, defined as initial infusion OR less than 3 months since initial ocrelizumab infusion, OR
 - b. The patient is receiving the first infusion after at least a one-month gap in therapy outside of the approved dosing interval for drugs requiring every 6 months dosing duration (i.e. at least seven months of no ocrelizumab infusions), OR
 - d. Requirement of a change in ocrelizumab product, OR
3. Members who do not meet the criteria above are appropriate for ocrelizumab administration in a **home-based infusion** or physician office setting with or without supervision by a certified healthcare professional. Inpatient and hospital outpatient infusion, in the absence of the criteria in #1 or #2 above is considered not medically necessary.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: J2350

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Ocrelizumab (Ocrevus®)

Ocrevus (ocrelizumab) injection: Prescribing label. Genentech Inc.

https://www.gene.com/download/pdf/ocrevus_prescribing.pdf. Accessed May 17, 2017.

Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, Lublin F, Montalban X, Rammohan KW, Selmaj K, Traboulsee A, Wolinsky JS, Arnold DL, Klingelschmitt G, Masterman D, Fontoura P, Belachew S, Chin P, Mairon N, Garren H, Kappos L; OPERA I and OPERA II Clinical Investigators.. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. *N Engl J Med*. 2017 Jan 19;376(3):221-234. doi: 10.1056/NEJMoa1601277. Epub 2016 Dec 21.

Montalban X, Hauser SL, Kappos L, Arnold DL, Bar-Or A, Comi G, de Seze J, Giovannoni G, Hartung HP, Hemmer B, Lublin F, Rammohan KW, Selmaj K, Traboulsee A, Sauter A, Masterman D, Fontoura P, Belachew S, Garren H, Mairon N, Chin P, Wolinsky JS; ORATORIO Clinical Investigators.. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. *N Engl J Med*. 2017 Jan 19;376(3):209-220. doi: 10.1056/NEJMoa1606468. Epub 2016 Dec 21.

Specialty Matched Consultant Advisory Panel – 5/23/18

Genentech, Inc. Ocrevus (ocrelizumab) injection for intravenous use. Highlights of prescribing information. November 2018. Available at:

https://www.gene.com/download/pdf/ocrevus_prescribing.pdf. Accessed April 2019.

Specialty Matched Consultant Advisory Panel – 5/15/19

Genentech, Inc. Ocrevus (ocrelizumab) injection for intravenous use. Highlights of prescribing information. July 2019. Available at: https://www.gene.com/download/pdf/ocrevus_prescribing.pdf. Accessed August 2019.

Medical Director review 9/2019

Genentech, Inc. Ocrevus (ocrelizumab) injection for intravenous use. Highlights of prescribing information. November 2019. Available at:

https://www.gene.com/download/pdf/ocrevus_prescribing.pdf. Last accessed May 2020.

Specialty Matched Consultant Advisory Panel – 5/20/20

Policy Implementation/Update Information

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| 6/15/17 | New policy developed. Ocrelizumab may be considered medically necessary for the treatment of relapsing multiple sclerosis or primary progressive multiple sclerosis when criteria are met. (sk) |
| 6/30/17 | Added C9399 to Billing/Coding section. (sk) |
| 12/29/17 | Code J2350 added to Billing/Coding section for effective date 1/1/2018. Codes J3490, J3590, and C9399 deleted from Billing/Coding section for effective date 12/31/2017. (sk) |
| 1/1/2018 | Site of care criteria added to Policy Guidelines. Policy notification given 1/1/2018 for effective date 4/1/2018. (sk) |
| 6/8/18 | Specialty Matched Consultant Advisory Panel review 5/23/18. No change to policy intent. (krc) |
| 5/28/19 | Updated Policy Guidelines section with vaccination recommendations for live and live-attenuated vaccinations prior to initiation of Ocrevus. Reference added. Specialty |

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Matched Consultant Advisory Panel review 5/15/2019. No change to policy intent. (krc)

- 9/10/19 Updated “When Covered” section with the following clarification for relapsing forms of multiple sclerosis: “(to include clinically isolated syndrome, relapsing-remitting disease and active secondary progressive disease).” Reference added. Medical Director review 9/2019. (krc)
- 6/23/20 Updated Policy Guidelines to include risk and management of infusion-related reactions. Reference added. Specialty Matched Consultant Advisory Panel review 5/20/2020. (krc)
- 8/11/20 Updated SOC criteria in “Policy Guidelines” section from “first infusion OR less than 3 months since first infusion” to “the patient is new to therapy, defined as initial infusion OR less than 3 months since initial infusion” for clarity. Added the following to SOC criteria: “first infusion after at least a one-month gap in therapy outside of the approved dosing interval for drugs requiring every 6 months dosing duration (i.e. at least seven months of no ocrelizumab infusions)”. **Notification given 8/11/2020 for effective date 10/13/2020.** (krc)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.