Ocrevus® (Ocrelizumab)

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Instructions for Use

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Commercial Policy
• Ocrevus® (Ocrelizumab)

Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Indiana	Refer to the state's Medicaid clinical policy
Kansas	Refer to the state's Medicaid clinical policy
Louisiana	Refer to the state's Medicaid clinical policy
North Carolina	None
Ohio	Ocrevus® (Ocrelizumab) (for Ohio Only)
Pennsylvania	Refer to the state's Medicaid clinical policy
Washington	Refer to the state's Medicaid clinical policy

Coverage Rationale

Primary Progressive Multiple Sclerosis

Ocrevus is proven and medically necessary for the treatment of primary progressive multiple sclerosis (PPMS) when all of the following criteria are met:

- For initial therapy, **all** of the following;
  - Diagnosis of primary progressive multiple sclerosis (PPMS); and
  - Patient is not receiving Ocrevus in combination with **any** of the following:
    - Disease modifying therapy (e.g., interferon beta preparations, dimethyl fumarate, glatiramer acetate, natalizumab, fingolimod, cladribine, siponimod, or teriflunomide); or
    - B cell targeted therapy (e.g., rituximab, belimumab, ofatumumab, ublituximab-xiiy); or
    - Lymphocyte trafficking blockers (e.g., alemtuzumab, mitoxantrone)

    and
  - Ocrevus dosing is in accordance with the United States Food and Drug Administration approved labeling; and
  - Initial authorization is for no more than 12 months

- For **continuation of therapy**, **all** of the following:
  - Patient has previously received treatment with Ocrevus; and
  - Documentation of positive clinical response to Ocrevus therapy; and
  - Patient is not receiving Ocrevus in combination with **any** of the following:
    - Disease modifying therapy (e.g., interferon beta preparations, dimethyl fumarate, glatiramer acetate, natalizumab, fingolimod, cladribine, siponimod, or teriflunomide); or
    - B cell targeted therapy (e.g., rituximab, belimumab, ofatumumab, ublituximab-xiiy); or
    - Lymphocyte trafficking blockers (e.g., alemtuzumab, mitoxantrone)

    and
  - Ocrevus dosing is in accordance with the United States Food and Drug Administration approved labeling; and
  - Authorization is for no more than 12 months

Relapsing Forms of Multiple Sclerosis

Ocrevus is proven and medically necessary for the treatment of relapsing forms of multiple sclerosis (MS) when the following criteria are met:

- For **initial therapy**, **all** of the following:
  - Diagnosis of relapsing forms of multiple sclerosis (MS) (e.g., relapsing-remitting MS, secondary-progressive MS with relapses, progressive-relapsing MS with relapses); and
  - **Both** of the following:
    - Submission of medical records (e.g., chart notes, laboratory values, etc.) documenting either a history of intolerance or severe adverse event to rituximab or a contraindication to rituximab that would not be applicable to Ocrevus; and
    - Physician attests that, in their clinical opinion, the same intolerance or severe adverse event would not be expected to occur with Ocrevus; and
    - Rituximab Step Therapy only applies to the following states: **AZ, NJ, NY, OH, RI,** and **TN**
  - Patient is not receiving Ocrevus in combination with **any** of the following:
    - Disease modifying therapy (e.g., interferon beta preparations, glatiramer acetate, natalizumab, fingolimod, cladribine, siponimod, or teriflunomide); or
    - B cell targeted therapy (e.g., rituximab, belimumab, ofatumumab, ublituximab-xiiy); or
    - Lymphocyte trafficking blockers (e.g., alemtuzumab, mitoxantrone)

    and
  - Ocrevus dosing is in accordance with the United States Food and Drug Administration approved labeling; and
  - Initial authorization is for no more than 12 months
- For **continuation of therapy**, **all** of the following:
  - Patient has previously received treatment with Ocrevus; and
  - Documentation of positive clinical response to Ocrevus therapy; and
  - Patient is not receiving Ocrevus in combination with **any** of the following:
    - Disease modifying therapy (e.g., interferon beta preparations, dimethyl fumarate, glatiramer acetate, natalizumab, fingolimod, cladribine, siponimod, or teriflunomide); or
    - B cell targeted therapy (e.g., rituximab, belimumab, ofatumumab, ublituximab-xiiy); or
    - Lymphocyte trafficking blockers (e.g., alemtuzumab, mitoxantrone)

    and
  - Ocrevus dosing is in accordance with the United States Food and Drug Administration approved labeling; and
  - Authorization is for no more than 12 months

Ocrevus is unproven and not medically necessary for the treatment of:

- Lupus nephritis[12]
- Rheumatoid arthritis[8-11]
- Systemic lupus erythematosus[13]

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service.

Benefit coverage for health services is determined by federal, state, or contractual requirements 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 Code	Description
J2350	Injection, ocrelizumab, 1 mg

Diagnosis Code	Description
G35	Multiple sclerosis

Background

Ocrelizumab is a humanized monoclonal antibody designed to selectively target CD20-positive B cells. CD20-positive B cells are a specific type of immune cell thought to be a key contributor to myelin (nerve cell insulation and support) and axonal (nerve cell) damage, which can result in disability in people with multiple sclerosis. Ocrelizumab binds to CD20 cell surface proteins expressed on certain B cells, but not on stem cells or plasma cells, and therefore important functions of the immune system may be preserved.[1]

Clinical Evidence

Proven

Primary Progressive Multiple Sclerosis (PPMS)

The Phase 3 ORATORIO study was a multicenter, randomized, double-blind, placebo-controlled, global study evaluating the efficacy and safety of ocrelizumab in patients with primary progressive multiple sclerosis. A total of 732 patients were randomized to receive ocrelizumab 600 mg IV or placebo every 24 weeks. ORATORIO met its primary endpoint, showing treatment with ocrelizumab significantly reduced the risk of 12-week confirmed disability progression (as measured by the Expanded Disability Status Scale) by 24% compared with placebo ($p = 0.0321$). Ocrelizumab also significantly reduced the risk of 24-week confirmed disability progression by 25% vs. placebo ($p = 0.0365$). Overall, the incidence of adverse events was similar between ocrelizumab and placebo. The most common adverse events were mild-to-moderate infusion-related reactions. The incidence of serious adverse events, including serious infections, was also similar between ocrelizumab and placebo. In a subgroup analysis of the ORATORIO study, the efficacy of ocrelizumab vs. placebo in patients with and without T1 gadolinium-enhancing lesions at baseline was consistent with that in the overall study population. However, the ORATORIO study was not powered to demonstrate efficacy differences between these subgroups. The authors concluded that among patients with primary progressive multiple sclerosis, ocrelizumab was associated with lower rates of clinical and MRI progression than placebo. Extended observation is required to determine the long-term safety and efficacy of ocrelizumab.[14]

Relapsing Forms of Multiple Sclerosis (RMS)

The Phase 3 OPERA I and OPERA II studies were randomized, double-blind, double-dummy, parallel-group studies evaluating the efficacy and safety of ocrelizumab 600 mg every 24 weeks vs. interferon beta-1a 44 mcg three times weekly, in patients with relapsing forms of multiple sclerosis. Relapsing forms of multiple sclerosis include patients with relapsing-remitting multiple sclerosis or those with secondary progressive multiple sclerosis who continued to experience relapses. Both the OPERA I and OPERA II studies met their primary and major secondary endpoints. Treatment with ocrelizumab significantly reduced the protocol-defined annualized relapse rate at 96 weeks vs. interferon beta-1a by 46% in OPERA I ($p < 0.0001$) and by 47% in OPERA II ($p < 0.0001$). In a pooled analysis of OPERA I and II, ocrelizumab treatment also significantly reduced the time to onset of both 12-week and 24-week confirmed disability progression vs. interferon beta-1a by 40% for both time points ($p = 0.0006$ and $p = 0.0025$, respectively). The incidence of adverse events and serious adverse events, including serious infections, was similar between ocrelizumab and interferon beta-1a in both studies. The most common adverse events were mild-to-moderate infusion-related reactions. The authors concluded that among patients with relapsing multiple sclerosis, ocrelizumab was associated with lower rates of disease activity and progression than interferon beta-1a over a period of 96 weeks. Larger and longer studies of the safety of ocrelizumab are required.[15]

Unproven

Lupus Nephritis

Mysler et al. conducted a Phase 3, randomized, double-blind, placebo-controlled, parallel-group trial (BELONG), to evaluate the safety and efficacy of ocrelizumab in patients with active, proliferative Class 3/4 lupus nephritis.[12] Patients were randomized to receive placebo, ocrelizumab 400 mg or ocrelizumab 1,000 mg IV on days 1 and 15, followed by a single infusion at Week 16 and every 16 weeks thereafter. All patients received standard of care (mycophenolate mofetil or cyclophosphamide followed by azathioprine) and were also permitted to receive IV or oral steroids. The primary endpoint was the ORR (CRR and PRR) at Week 48. Efficacy outcomes at Week 48 were analyzed for patients who were treated for ≥ 32 weeks prior to study termination (n = 223). At Week 48 the ORR rates were 66.7% and 67.1% in the ocrelizumab 400 mg (n = 75) and 1,000 mg groups (n = 73), respectively, vs. 54.7% in the placebo group (n = 75). The associated treatment difference vs placebo was 12.1% (95% CI -3.3 to 27.5) for the ocrelizumab 400 mg group and 13.9% (95% CI -1.4 to 29.2) for the 1,000 mg group. The combined ORR for the 2 ocrelizumab groups was 66.9% with an associated treatment difference of 12.7% (95% CI -0.8 to 26.1) vs. placebo. An imbalance in the rate of serious and opportunistic infections in ocrelizumab-treated patients led to an early termination of the study. Patients continued into safety follow-up.

Rheumatoid Arthritis

Due to the conclusion that the benefit to risk profile was not favorable, the manufacturer of ocrelizumab has discontinued the clinical program for rheumatoid arthritis. The manufacturer has taken into account the currently available treatment options. An infection safety signal was detected which included serious infections, some of which were fatal, and opportunistic infections.

The ocrelizumab clinical studies for RA included 4 Phase 3 studies (STAGE, SCRIPT, FILM, and FEATURE). STAGE (DMARD inadequate response population) and SCRIPT (anti-TNF inadequate response population) were 48-week randomized, double-blind, placebo-controlled, parallel group studies, followed by an open-label extension period. During the double-blind treatment periods, patients received 2 courses of ocrelizumab at 6-month intervals (each course consisted of 2 infusions of ocrelizumab 200 mg or 500 mg IV on days 1 and 15 and Weeks 24 and 26). The patients also received traditional DMARD(s) as background therapy.[8-11]

FILM was a 2-year double-blind, placebo-controlled, parallel group study, followed by an open-label extension period.[11] The patients in this study were MTX-naive. Patients received MTX alone or a course of ocrelizumab (2 infusions of 200 mg or 500 mg, with retreatment every 6 months) plus MTX. FEATURE was a 24-week randomized, double-blind, placebo-controlled, parallel group study, followed by a 24 week double-blind period (not placebo-controlled) and an extension period. The patients in this study had a previous inadequate response to treatment with DMARDs or biologics. Patients received MTX as background therapy, and a single infusion of ocrelizumab 400 mg on day 1 and placebo on day 15, or ocrelizumab 200 mg IV on days 1 and 15, or placebo infusions on days 1 and 15.

Systemic Lupus Erythematosus

Md Yusof et al. conducted an observational study of 88 patients with SLE who were treated with 2 infusions of rituximab 1,000 mg repeated upon clinical relapse. Patients who had features of HACA were given ocrelizumab 1,000 mg IV x 2 or a rituximab desensitizing regimen.[13] Response was defined as improvement to ≤ 1 persistent BILAG B and no A/B flare. Of the 76 (86%) primary responders, 63 were retreated with rituximab upon relapse. Of these, 54 continued to respond [median (IQR) time-to-CI-relapse: 54 (37-93) weeks] while 9 were secondary non-responders [median (IQR) time-to-CI-relapse: 62 (47-95) weeks]. 8 of the 9 secondary non-responders were due to HACA, 3 of whom were treated with ocrelizumab. All 3 patients who were treated with ocrelizumab had a response and complete peripheral B cell depletion. One secondary non-responder was desensitized with rituximab and continued to experience HACA.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Ocrevus is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease), or primary progressive multiple sclerosis.[16]

References

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Policy History/Revision Information

Date	Summary of Changes
05/01/2024	**Coverage Rationale** • Changed duration for initial authorization from "no more than ***6*** months" to "no more than ***12*** months" **Supporting Information** • Updated *References* section to reflect the most current information • Archived previous policy version CS2023D0056R

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.