

# OCREVUS™ (OCRELIZUMAB)

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Related Policies
<ul style="list-style-type: none"> <li>• <a href="#">Injectable Chemotherapy Drugs: Application of NCCN Clinical Practice Guidelines</a></li> <li>• <a href="#">Specialty Medication Administration - Site of Care Review Guidelines</a></li> <li>• <a href="#">Specialty Pharmacy for Certain Specialty Medications Administered in an Outpatient Hospital Setting</a></li> </ul>

## INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines 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.

## CONDITIONS OF COVERAGE

Applicable Lines of Business/Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General Benefits Package
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	Yes - Home Yes - Outpatient <sup>3</sup> Yes <sup>2</sup> - Office
Precertification with Medical Director Review Required	Yes <sup>1,3</sup>
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	Home, Outpatient <sup>4</sup> , Office
Special Considerations	<sup>1</sup> Precertification with review by a Medical Director or their designee through Oxford's Medical Management is required. <sup>2</sup> <b>Participating Providers in the Office Setting:</b> Precertification is required for services performed in the office of a participating provider.

Special Considerations  
(continued)

**Non-Participating/Out-of-Network Providers in the Office Setting:** Precertification is not required, but is encouraged for out-of-network services performed in the office. If precertification is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered.

<sup>3</sup>Additional precertification requirements apply to requests for hospital outpatient facility infusion of Ocrevus™; refer to the policy titled [Specialty Medication Administration - Site of Care Review Guidelines](#).

<sup>4</sup>Participating hospitals are required to purchase Ocrevus™ (ocrelizumab) from the BriovaRx Specialty Pharmacy when the medication is administered in an outpatient hospital setting; refer to the policy titled [Specialty Pharmacy for Certain Specialty Medications Administered in an Outpatient Hospital Setting](#) for additional information.

## BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member-specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to: Acquired Rare Disease Drug Therapy Exception Process.

### **Essential Health Benefits for Individual and Small Group**

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

## COVERAGE RATIONALE

Please refer to the policy titled [Injectable Chemotherapy Drugs: Application of NCCN Clinical Practice Guidelines](#) for updated information based upon the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium® (NCCN Compendium®) for oncology indications.

### **Ocrevus (ocrelizumab) is proven for:**

- **Primary Progressive Multiple Sclerosis<sup>16</sup>**  
**Ocrevus is medically necessary for the treatment of primary progressive multiple sclerosis (PPMS) when ALL of the following criteria are met:**
  - Diagnosis of primary progressive multiple sclerosis (PPMS); **and**
  - **One** of the following:
    - **Initial therapy** for ocrelizumab when meeting both of the following:
      - Patient is **not** receiving ocrelizumab in combination with **any** of the following:
        - Disease modifying therapy (e.g., interferon beta preparations, daclizumab, dimethyl fumarate, glatiramer acetate, natalizumab, fingolimod, or teriflunomide)
        - B cell targeted therapy (e.g., rituximab, belimumab, ofatumumab)
        - Lymphocyte trafficking blockers (e.g., alemtuzumab, mitoxantrone)
      - and**
      - Initial dosing: One time 300 mg intravenous course of doses on days 1 and 15.
- or**

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

**and**

  - Continued dosing: One 600 mg intravenous dose every 6 months.
  
- **Relapsing Forms of Multiple Sclerosis<sup>16</sup>**  
**Ocrevus is medically necessary for the treatment of relapsing forms of multiple sclerosis (MS) when BOTH of the following criteria are met:**
  - Diagnosis of relapsing forms of multiple sclerosis (MS) (e.g., relapsing-remitting MS, secondary-progressive MS with relapses, progressive-relapsing MS with relapses); **and**
  - **One** of the following:
    - **Initial therapy** for ocrelizumab meeting **all** of the following:
      - Patient has history of failure following a trial for at least 4 weeks **or** history of intolerance or contraindication to **one** of the following:
        - interferon  $\beta$ -1a (Avonex<sup>®</sup>, Rebif<sup>®</sup>, Plegridy<sup>™</sup>)
        - interferon  $\beta$ -1b (Betaseron<sup>®</sup> or Extavia<sup>®</sup>)
        - glatiramer acetate (Copaxone<sup>®</sup>, Glatopa<sup>®</sup>)
        - dimethyl fumarate (Tecfidera<sup>®</sup>)
        - teriflunomide (Aubagio<sup>®</sup>)
        - fingolimod (Gilenya<sup>®</sup>)
        - alemtuzumab (Lemtrada<sup>®</sup>)
        - natalizumab (Tysabri<sup>®</sup>)

**and**

      - Patient is **not** receiving ocrelizumab in combination with **any** of the following:
        - Disease modifying therapy (e.g., interferon beta preparations, daclizumab, glatiramer acetate, natalizumab, fingolimod, or teriflunomide)
        - B cell targeted therapy (e.g., rituximab, belimumab, ofatumumab)
        - Lymphocyte trafficking blockers (e.g., alemtuzumab, mitoxantrone)

**and**

      - Initial dosing: One time 300 mg intravenous course of doses on days 1 and 15.
    - or**
    - **Continuation therapy** for ocrelizumab when meeting **all** of the following:
      - Patient has previously received treatment with ocrelizumab; **and**
      - Documentation of positive clinical response to ocrelizumab therapy; **and**
      - Patient is **not** receiving ocrelizumab in combination with **any** of the following:
        - Disease modifying therapy (e.g., interferon beta preparations, daclizumab, dimethyl fumarate, glatiramer acetate, natalizumab, fingolimod, or teriflunomide)
        - B cell targeted therapy (e.g., rituximab, belimumab, ofatumumab)
        - Lymphocyte trafficking blockers (e.g., alemtuzumab, mitoxantrone)

**and**

      - Continued dosing: One 600 mg intravenous dose every 6 months.

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

- Lupus nephritis<sup>12</sup>
- Rheumatoid arthritis<sup>8-11</sup>
- Systemic lupus erythematosus<sup>13</sup>

**U.S. FOOD AND DRUG ADMINISTRATION**

Ocrevus is indicated for the treatment of adult patients with relapsing or primary progressive forms of multiple sclerosis.<sup>16</sup>

**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.<sup>1</sup>

## 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 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 may apply.

HCPCS Code	Description
J2350	Injection, ocrelizumab, 1 mg

ICD-10 Diagnosis Code	Description
G35	Multiple sclerosis

## CLINICAL EVIDENCE

### **Proven/Medically Necessary**

#### ***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.<sup>14</sup>

#### ***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.<sup>15</sup>

### **Unproven/Not Medically Necessary**

#### ***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.<sup>12</sup> 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  $\geq 32$  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.<sup>8-11</sup>

FILM was a 2-year double-blind, placebo-controlled, parallel group study, followed by an open-label extension period.<sup>11</sup> 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.<sup>13</sup> Response was defined as improvement to  $\leq 1$  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). Eight 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.

## **REFERENCES**

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare Pharmacy, Clinical Pharmacy Program that was researched, developed and approved by the UnitedHealth Group National Pharmacy & Therapeutics Committee. [2018D0056D]

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#### POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
12/01/2018	<ul style="list-style-type: none"> <li>• Updated conditions of coverage/special considerations; modified notation to clarify:               <ul style="list-style-type: none"> <li>○ For <b>participating providers in the office setting</b>: Precertification is required for services performed in the office of a participating provider</li> <li>○ For <b>non-participating/out-of-network providers in the office setting</b>: Precertification is not required, but is encouraged for out-of-network services performed in the office; if precertification is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered</li> </ul> </li> <li>• Revised coverage rationale:               <ul style="list-style-type: none"> <li>○ Updated medical necessity criteria for initial treatment of relapsing forms of multiple sclerosis (MS); modified list of drug products to which the patient must demonstrate treatment failure (following a trial for at least 4 weeks) contraindication, or intolerance:                   <ul style="list-style-type: none"> <li>▪ Modified brand name listings for glatiramer acetate; added "Glatopa<sup>®</sup>"</li> <li>▪ Removed daclizumab (Zinbryta<sup>™</sup>)</li> </ul> </li> </ul> </li> <li>• Updated supporting information to reflect the most current references</li> <li>• Archived previous policy version PHARMACY 290.5 T2</li> </ul>