09-J2000-78

Original Effective Date: 06/15/17

Reviewed: 10/11/23

Revised: 11/15/23

Subject: Ocrelizumab (Ocrevus®) Infusion

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Multiple sclerosis (MS) is a chronic disease affecting the central nervous system (CNS). It is characterized by inflammation, demyelination, and scarring of the central nervous system and manifests as pathological (immune-mediated CNS demyelination and axonal injury) and clinical (exacerbations, disability progression) dissemination in time and space. MS has been categorized into four types: clinically isolated syndrome (CIS), relapsing-remitting (RRMS), secondary progressive (SPMS), and primary progressive (PPMS). The most common type is RRMS, which is characterized by acute attacks followed by periods of remission. An initial attack may present as a clinically isolated syndrome (CIS); individuals presenting with this syndrome are high risk for subsequent conversion to clinically definite MS (CDMS) when coupled with MRI lesions consistent with MS. Although a cure for MS remains elusive, several treatment options slow the progression of the disease and reduce the frequency of relapses.

Ocrelizumab (Ocrevus®) has been Food and Drug Administration (FDA) approved for the treatment primary progressive MS and of relapsing forms of MS to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults. Ocrelizumab is a humanized monoclonal antibody that is directed against CD20-expressing B-cells. The exact mechanism is unknown, but it is expected to interfere with antibody-dependent and complement-mediated cytotoxicity. In 2018, the American Academy of Neurology published a practice guideline on the use of disease-modifying therapy for adults with multiple sclerosis which includes an assessment of the effectiveness and safety of ocrelizumab in the treatment of MS. Ocrelizumab has demonstrated a reduction in measures of disease activity including clinical relapse rate, new and enlarging T2 lesions, and disability progression in patients with relapsing MS. It has also demonstrated a reduction in disability progression in patients with primary progressive MS.

Ocrelizumab was evaluated in patients with relapsing MS in two identical randomized, double-blind, active-controlled phase 3 trials. Ocrelizumab 600 mg intravenous infusion every 24 weeks was compared to interferon beta-1a (Rebif) 44 mcg three times weekly subcutaneous injection. The primary endpoint was the Annualized Relapse Rate (ARR) at 96 weeks. There was a significant reduction in the ARR in both trials with ocrelizumab as compared to interferon beta-1a (0.16 vs 0.29, p<0.001). Additionally, ocrelizumab demonstrated a significant reduction in the percentage of patients with disability progression confirmed at 12 weeks (9.1% vs 13.6%, p<0.001) and 24 weeks (6.9% vs 10.5%, p=0.003). The mean number of T1 gadolinium-enhancing lesions and T2 hyperintense lesions on MRI were lower in the ocrelizumab treatment groups as compared to interferon-beta-1a. The most common adverse reactions with ocrelizumab were infusion reaction (34.3%), nasopharyngitis, upper respiratory tract infection, headache, and urinary tract infection. Neoplasms occurred more commonly with ocrelizumab as compared to interferon beta-1a (0.5% vs 0.2%).

Ocrelizumab was evaluated in 732 patients with primary progressive multiple sclerosis in a phase 3, randomized, double-blind, placebo-controlled trial for at least 120 weeks and until a prespecified number of confirmed disability progression events occurred. The percentage of patients with disability progression confirmed at 12 weeks was the primary end point. Ocrelizumab had fewer patients with 12-week confirmed disability progression as compared to placebo (32.9% vs 39.3%, p=0.03). Secondary endpoints of 24-week confirmed disability progression, ambulation speed, total volume of brain lesions on T2-weighted lesions and change in brain volume were all significantly improved with ocrelizumab as compared to placebo. There was no difference in the 36 item Short-form Health Survey (SF-36) between groups. Infusion reactions and upper respiratory infection occurred more commonly with ocrelizumab. Neoplasms also occurred more frequently with ocrelizumab as compared to placebo (2.3% vs 0.8%).

POSITION STATEMENT:

Site of Care: If ocrelizumab (Ocrevus) is administered in a hospital-affiliated outpatient setting, additional requirements may apply depending on the member's benefit. Refer to 09-J3000-46: Site of Care Policy for Select Specialty Medications.

I. Initiation of ocrelizumab (Ocrevus) **meets the definition of medical necessity** when **ALL** of the following are met:
    1. Multiple Sclerosis (MS)
        a. Member meets **ONE** of the following:
            i. Member is diagnosed with Primary Progressive MS
            ii. Member is diagnosed with Relapsing-remitting MS [RRMS], active secondary-progressive MS [SPMS], or first clinical episode and has MRI features consistent with MS and **ONE** of the following is met:
                1. **ONE** of the following (a, b, or c):
                    a. The patient has highly active MS disease activity and **BOTH** of the following:
                        i. The patient has ≥ 2 relapses in the previous year
                        ii. **ONE** of the following:

1. The patient has ≥ 1 gadolinium enhancing lesion on MRI
2. The patient has significant increase in T2 lesion load compared with a previous MRI

b. The patient has been treated with at least 3 MS agents from different drug classes

c. **ONE** of the following (i, ii, iii, or iv):

i. The patient has tried and had an inadequate response to dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan, Glatopa), **OR** teriflunomide (generic)

ii. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan, Glatopa), **OR** teriflunomide (generic)

iii. The patient has a FDA labeled contraindication to dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan, Glatopa), **AND** teriflunomide (generic)

iv. The prescriber has provided information in support of using the requested agent over both dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan, Glatopa), **AND** teriflunomide (generic)

b. Member has been screened for hepatitis B virus and does not have an active hepatitis B virus infection

c. Ocrelizumab will **NOT** be used in combination with **ANY** of the following:

i. Alemtuzumab (Lemtrada)
ii. Cladribine (Mavenclad)
iii. Dimethyl fumarate (Tecfidera)
iv. Diroximel fumarate (Vumerity)
v. Fingolimod (Gilenya, Tascenso ODT)
vi. Glatiramer acetate (Copaxone, Glatopa)
vii. Interferon beta-1a (Avonex, Rebif)
viii. Interferon beta-1b (Betaseron, Extavia)
ix. Mitoxantrone (Novantrone)
x. Monomethyl fumarate (Bafiertam)
xi. Natalizumab (Tysabri)
xii. Ofatumumab (Kesimpta)
xiii. Ozanimod (Zeposia)
xiv. Peg-interferon beta-1a (Plegridy)

xv. Ponesimod (Ponvory)
xvi. Rituximab (Rituxan or biosimilars)
xvii. Siponimod (Mayzent)
xviii. Teriflunomide (Aubagio)
xix. Ublituximab (Briumvi)

d. The dose does not exceed 600 mg every 6 months*

*The first dose is given as a 300 mg infusion on day 1 and 15

Approval duration: 1 year

II. Continuation of ocrelizumab (Ocrevus) **meets the definition of medical necessity** for the treatment of multiple sclerosis when **ALL** of the following are met:

1. Ocrelizumab will **NOT** be used in combination with **ANY** of the following:
    a. Alemtuzumab (Lemtrada)
    b. Cladribine (Mavenclad)
    c. Dimethyl fumarate (Tecfidera)
    d. Diroximel fumarate (Vumerity)
    e. Fingolimod (Gilenya, Tascenso ODT)
    f. Glatiramer acetate (Copaxone, Glatopa)
    g. Interferon beta-1a (Avonex, Rebif)
    h. Interferon beta-1b (Betaseron, Extavia)
    i. Mitoxantrone (Novantrone)
    j. Monomethyl fumarate (Bafiertam)
    k. Natalizumab (Tysabri)
    l. Ofatumumab (Kesimpta)
    m. Ozanimod (Zeposia)
    n. Peg-interferon beta-1a (Plegridy)
    o. Ponesimod (Ponvory)
    p. Rituximab (Rituxan or biosimilars)
    q. Simponimod (Mayzent)
    r. Teriflunomide (Aubagio)
    s. Ublituximab (Briumvi)
2. Member has demonstrated a beneficial response to therapy
3. Authorization/reauthorization for ocrelizumab has been previously approved by Florida Blue or another health plan in the past 2 years, **OR** the member currently meets all indication-specific initiation criteria
4. The dose does not exceed 600 mg every 6 months

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

Administration should be provided by a healthcare professional with access to appropriate medical support to manage severe reactions such as serious infusion reactions. Pre-medicate with methylprednisolone (or an equivalent corticosteroid) and an antihistamine (e.g., diphenhydramine) prior to each infusion. Hepatitis B virus and quantitative serum immunoglobulin screening are required before the first dose.

- Initial dose: 300 mg intravenous infusion, followed two weeks later by a second 300 mg intravenous infusion.
- Subsequent doses: single 600 mg intravenous infusion every 6 months.
- Observe the patient for at least one hour after the completion of the infusion

Dose Adjustments

Dose modifications in response to infusion reactions depend on the severity.

Life-threatening Infusion Reactions: Immediately stop and permanently discontinue if there are signs of a life-threatening or disabling infusion reaction.

Severe Infusion Reactions: Immediately interrupt the infusion and administer appropriate supportive treatment, as necessary. Restart the infusion only after all symptoms have resolved. See prescribing information for restarting dose.

Mild to Moderate Infusion Reactions: Reduce the infusion rate to half the rate at the onset of the infusion reaction and maintain the reduced rate for at least 30 minutes. See prescribing information for dose increase.

Drug Availability

- 300 mg/10 mL in a single dose vial

PRECAUTIONS:

Contraindications

- Active hepatitis B virus infection
- History of life-threatening infusion reaction to ocrelizumab

Precautions/Warnings

- Infusion reactions: Management recommendations for infusion reactions depend on the type and severity of the reaction. Permanently discontinue if a life-threatening or disabling infusion reaction occurs
- Infections: Delay administration in patients with an active infection until the infection is resolved. Vaccination with live-attenuated or live vaccines is not recommended during treatment with and after discontinuation, until B-cell repletion
- Progressive Multifocal Leukoencephalopathy (PML): Withhold at the first sign or symptom suggestive of PML.
- Reduction in Immunoglobulins: Monitor the level of immunoglobulins at the beginning of treatment. Monitor during and after discontinuation of treatment, until B-cell repletion, and especially when recurrent serious infections are suspected. Consider discontinuing in patients with serious opportunistic or recurrent serious infections, and if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins
- Malignancies: An increased risk of malignancy, including breast cancer may exist
- Immune-Mediated Colitis: Immune-mediated colitis has been reported in the post-marketing setting. Monitor and evaluate promptly if colitis is suspected.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J2350	Injection, ocrelizumab, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

G35	Multiple sclerosis

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the guideline creation. The Site of Care Policy for Select Specialty Medications does not apply to Medicare Advantage members.

DEFINITIONS:

Clinically isolated syndrome (CIS): the first clinical presentation of disease that shows characteristics of inflammatory demyelination that could be MS but has yet to fulfill criteria of dissemination in time.

Progressive multifocal leukoencephalopathy (PML): an opportunistic viral infection of the brain that usually leads to death or severe disability.

Primary-progressive multiple sclerosis (PPMS): Steadily progressive course from onset; occurs in 10-15% of patients with MS.

Relapsing-remitting multiple sclerosis (RRMS): Characterized by acute attacks followed by periods of remission; primary form of MS that occurs in approximately 85% of patients.

Secondary-progressive multiple sclerosis (SPMS): An initial period of RRMS, followed by a steadily progressive course, with acute relapses (active disease) or without acute relapses (not active disease); 75-85% of patients diagnosed with RRMS will transition to SPMS

RELATED GUIDELINES:

Alemtuzumab (Lemtrada), 09-J2000-27
Cladribine (Mavenclad), 09-J3000-34
Dimethyl Fumarate (Tecfidera), Diroximel fumarate (Vumerity) and Monomethyl fumarate (Bafiertam), 09-J1000-96
Fingolimod (Gilenya™), 09-J1000-30
Multiple Sclerosis Self Injectable Therapy, 09-J1000-39
Natalizumab (Tysabri®) IV, 09-J0000-73
Ofatumumab (Kesimpta), 09-J3000-84
Ozanimod (Zeposia), 09-J3000-70
Siponimod (Mayzent), 09-J3000-35
Teriflunomide (Aubagio), 09-J1000-82

OTHER:

None

REFERENCES:

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3. Hauser SL, Bar-Or A, Comi G et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med 2017; 376: 221-34.
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5. Montalban X, Hauser SL, Kappos L et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med 2017; 376:209-20.

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9. Rae-Grant A, Day GS, Marrie RA et al. Practice guideline: Disease-modifying therapies for adults with multiple sclerosis: Report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. April 2018. Available at: https://www.aan.com/Guidelines/home/GuidelineDetail/898.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 10/11/23.

GUIDELINE UPDATE INFORMATION:

06/15/17	New Medical Coverage Guideline.
01/01/18	Annual HCPCS coding update: added HCPCS code J2350
12/15/18	Review and revision to guideline; consisting of updating position statement and references.
11/11/19	Revision to guideline consisting of adding a reference to the Site of Care Policy for Select Specialty Medications and updating the Program Exceptions.
11/15/19	Review and revision to guideline; consisting of updating position statement, description, and references.
07/01/20	Revision to guideline consisting of updating the position statement.
10/01/20	Revision to guideline consisting of updating the position statement.
03/15/21	Revision to guideline consisting of updating the position statement.
06/15/22	Review and revision to guideline; consisting of updating the position statement.
10/15/22	Review and revision to guideline; consisting of updating warnings and references.
01/01/23	Review and revision to guideline; consisting of updating the position statement to include generic fingolimod as a preferred generic.
05/15/23	Revision to guideline; consisting of updating the position statement to include generic teriflunomide as a preferred generic and removal of Aubagio as a preferred brand. Updated list of agents not to be used in combination.
11/15/23	Review and revision to guideline; consisting of updating the position statement to include Glatopa.