MEDICAL MUTUAL®

MedicalPolicy

Policy:	**201708**	**Initial Effective Date: 04/27/2017**
Code(s):	**HCPCS J2350**	**Annual Review Date: 04/19/2018**
SUBJECT:	**Ocrevus ® (ocrelizumab)**	**Last Revised Date: 06/25/2018**

Prior approval is required for some or all procedure codes listed in this Corporate Medical Policy.

OVERVIEW

Ocrevus is a CD20-directed cytolytic antibody indicated for the treatment of patients with relapsing or primary progressive forms of multiple sclerosis (MS).[1]

The efficacy of Ocrevus in patients with relapsing MS was established in two identical, Phase III, multicenter, randomized, double-blind, double-dummy, active controlled, published, parallel group trials (OPERA I and OPERA II), that used Rebif® (interferon beta-1a subcutaneous [SC]) as an active comparator for up to 96 weeks.[2] Approximately 25% of patients had previously used MS disease-modifying therapy (mainly beta interferon or glatiramer acetate products). In these two trials (OPERA I n = 821 and OPERA II n = 825) the annualized relapse rate (ARR) among patients with relapsing MS was lower with Ocrevus in both studies compared with Rebif (0.16 vs. 0.29; P < 0.001). In a prespecified analysis the percentage of patients with disability progression confirmed at 12 weeks was significantly lower with Ocrevus compared with Rebif (9.1% vs. 13.6%; P < 0.001), as well as the percentage of patients with disability progression confirmed at 24 weeks (6.9% vs. 10.5%; P = 0.001). Several magnetic resonance imaging (MRI) parameters were also more favorable with Ocrevus vs. Rebif. The percentage of patients with no evidence of disease activity by Week 96, an exploratory endpoint, was also statistically significantly larger for patients given Ocrevus vs. Rebif (47.9% vs. 29.2%; P < 0.001).

The efficacy of Ocrevus in patients with primary progressive MS was established in one Phase III, randomized, parallel-group, double-blind, placebo-controlled published trial (ORATORIO [n = 732]).[3] Therapy duration was at least 120 weeks. Most patients (88%) had not previously used MS disease-modifying therapy. In ORATORIO the primary endpoint was the percentage of patients with disability progression confirmed as 12 weeks in a time-to-event analysis that defined disability progression as an increase in the Expanded Disability Status Scale (EDSS) of at least 1.0 point from baseline that was sustained on subsequent visits for at least 12 weeks if the baseline score was 5.5 or less or an increase of at least 0.5 points that was sustained for at least 12 weeks if the baseline EDSS score was more than 5.5. The percentage of patients with primary progressive MS with 12-week confirmed disability progression was 32.9% with Ocrevus vs. 39.3% with placebo (P = 0.03). The percentage of patients with 24-week confirmed disability progression was 29.6% with Ocrevus vs. 35.7% with placebo (P = 0.04). By Week 120, performance on the timed 25-foot walk worsened by 38.9% with Ocrevus vs. 55.1% with placebo (P = 0.04). More favorable MRI results on several parameters were also observed with Ocrevus compared with placebo.

MS is a chronic disabling disease of the central nervous system (CNS) characterized by inflammation, demyelination, and degenerative changes.[4-6] Patients experience relapses followed by remission of neurological symptoms.[5] MS lesions occur in many different parts of the CNS and the symptoms and clinical course of the disease are highly variable. Some common signs and symptoms of the disease include vision problems (e.g., nystagmus), ambulation problems, pain, fatigue, spasticity, cognitive dysfunction, depression, ataxia, sensory loss, bladder disturbances, bowel dysfunction, dizziness, and vertigo.[4] In general, patients with MS may have diminished ratings on vitality and physical functions.[5] Most people with MS are diagnosed between the ages of 20 and 50 years, but MS can manifest in young children and older adults.[4] Approximately 450,000 people are living with MS in the US.[5] In relapsing forms of MS women are impacted two to three times more commonly than men, and MS appears more predominant among Caucasians.

Four different clinical courses of MS have been delineated.[4-6] A relapse is defined as the development of new or recurring symptoms lasting at least 24 hours and separated from a previous attack by at least 1 month. Relapsing-remitting MS is characterized by acute attacks usually followed by almost complete recovery with limited progression. Disease progression is minimal between attacks. Approximately 85% of people are initially diagnosed with relapsing-remitting MS. Secondary-progressive MS begins as relapsing-remitting course but the disease transitions in many patients to a steadily progressive form with increased loss of function. Of the 85% of patients who initially have relapsing-remitting MS, more than 50% of patients will develop secondary-progressive MS within 10 years as will 90% of patients within 25 years. Primary progressive MS is noted by a steady decline in function from the onset without noted relapses. Around 10% to 15% of patients are diagnosed with primary progressive MS. Progressive-relapsing MS starts with disease progression at onset with occasional acute relapses and continued disease progression. Only a small minority of patients (< 5%) have progressive-relapsing MS. About 10% of the MS population has a benign disease course, which is generally determined retrospectively. Among those with relapsing forms of MS the severity, duration, and frequency of relapses vary widely among patients. The EDSS is the scale most often used to assess neurologic disability and evaluates cerebellar, pyramidal, brainstem, sensory, bowel, bladder, visual, and mental functional systems on a scale that ranges from 0 (normal neurologic examination) to 10 (death due to MS). MRI evaluations are used to assess current MS disease activity, as well as to monitor for permanent neurologic damage. Table 1 provides a comparison between relapsing MS and primary progressive MS.

Table 1. Relapsing MS vs. Primary Progressive MS.[4,6]

Characteristic	Relapsing MS	Primary Progressive MS
Percentage of the MS population	85% to 90%	10% to 15%
Clinical course	Recurrent subacute events of neurological dysfunction followed by complete or partial recovery.	Worsening of neurological dysfunction at disease onset with little or no recovery.
Age at onset	30 years of age	40 years of age
Gender	2:1 ratio of females to males	1:1 ratio of females to males
Disability prognosis	Generally can occur after many years.	Rapid progression of disability.
Inflammation/brain lesions	There is less inflammation with primary progressive MS. Also, patients with primary progressive MS have fewer brain lesions vs. relapsing MS and the lesions tend to contain fewer inflammatory cells.	
Systems impacted	Patients with primary progressive MS have relatively more issues with ambulation compared to patients with relapsing forms of MS.	

MS – Multiple sclerosis.

Therapies for Relapsing Forms of MS

Interferon beta therapies indicated for use in relapsing forms of MS include Avonex® (interferon beta-1a for intramuscular [IM] injection),[7] Rebif® (interferon beta 1-a for subcutaneous [SC] injection),[8] and Betaseron®/Extavia® (interferon beta-1b for SC injection).[9-10] Dosing of these products is IM once weekly (QW), SC three times weekly (TIW), and SC every other day, respectively. Plegridy™ (peginterferon beta-1a injection) is a pegylated interferon beta-1a product that is also indicated for the treatment of relapsing forms of MS and is dosed SC once every 14 days.[11] Another self-injectable MS therapy is Copaxone® (glatiramer acetate injection for SC use), which can be dosed SC either once daily (QD) or TIW.[12] Glatopa™ (glatiramer acetate injection for SC use) is the generic for Copaxone and is available in the 20 mg dose only.[13] Although some differences in efficacy have been observed in clinical trials among the interferon beta products, in general, these self-injectable MS therapies appear to reduce the ARR by approximately one-third.[14] Copaxone and several interferon beta products have been available for over 20 years with established efficacy and known safety. Oral therapies indicated in relapsing forms of MS include Aubagio® (teriflunomide tablets),[15] Gilenya™ (fingolimod capsules),[16] and Tecfidera™ (dimethyl fumarate delayed-release capsules).[17] Compared with placebo these agents lead to reductions in the ARR of approximately 31% with Aubagio, 54% with Gilenya, and 44% to 53% with Tecfidera. Tysabri® (natalizumab for IV infusion) is administered by IV infusion once every 4 weeks over 1 hour).[18] Tysabri is very effective (ARRs reduced by approximately 67%) but due to the risk of progressive multifocal leukoencephalopathy (PML) it must be used cautiously.[18] Lemtrada[19] (alemtuzumab injection for IV use) is indicated for use for the treatment of MS in patients with relapsing forms of MS but due to its safety profile it should be reserved for patients who have had an inadequate response to two or more medications indicated for the treatment of MS.[19] Lemtrada is given by IV infusion over 4 hours for two treatment courses: first course is 12 mg/day on 5 consecutive days and the second course is 12 mg/day on 3 consecutive days 12 months after the first treatment course. Lemtrada has a Boxed Warning regarding autoimmunity, infusion reactions, and malignancies.[19] Mitoxantrone injection is given as an IV infusion and once every 3 months (over 5 to 15 minutes), respectively but due to toxicities (e.g., cardiotoxicity, increased risk of developing secondary acute myeloid leukemia) the role of mitoxantrone is limited to a carefully selected MS patient population who have not responded to other therapies.[20]

Therapies for Primary Progressive MS

No other therapies are indicated for primary progressive MS. However, therapies have been investigated and used with mixed levels of results in patients with progressive forms of MS including broad-spectrum immunosuppressants (e.g., azathioprine, cyclophosphamide, cyclosporine), MS immunomodulators (e.g., Copaxone, beta interferons), monoclonal antibodies and other immunotherapies (Rituxan® [rituximab injection for IV use], Gilenya]) and other miscellaneous medications (e.g., epoetin alfa, dronabinol).[6] Among these agents, the most notable that have sizeable studies involving patients with primary progressive MS include Rituxan[22], Copaxone[23] and Gilenya[24].

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Ocrevus. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ocrevus as well as the monitoring required for adverse events (AEs) and long-term efficacy, initial approval requires Ocrevus to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration listed below. The Site of Care Medical Necessity Criteria applies to initial therapy and reauthorizations.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Ocrevus is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Relapsing Forms of Multiple Sclerosis (MS).** Approve for 1 year if the patient meets all of the following criteria (A, B, C, D and E):
   - **A)** The patient is ≥ 18 years of age; AND
   - **B)** The patient has a relapsing form of multiple sclerosis (MS) [relapsing forms of MS are relapsing-remitting MS {RRMS}, secondary-progressive MS {SPMS} with relapses, or progressive-relapsing MS {PRMS}] ; AND
   - **C)** The patient has previously tried at least one MS therapy including Avonex (interferon beta-1a), Rebif (interferon beta 1-a), Betaseron/Extavia (interferon beta-1b), Plegridy (peginterferon beta-1a), Copaxone/Glatopa (glatiramer acetate), Aubagio (teriflunomide tablets), Gilenya (fingolimod capsules), Tecfidera (dimethyl fumarate delayed-release capsules), Tysabri (Natalizumab) or Lemtrada (alemtuzumab); AND
   - **D)** Ocrevus is prescribed by, or in consultation with, a physician who specializes in the treatment of MS and/or a neurologist; AND
   - **E)** Site of care medical necessity is met*

   Ocrevus is indicated for the treatment of adult patients with relapsing or primary progressive forms of multiple sclerosis.[1] Many disease-modifying MS medications are available with established efficacy in relapsing forms of MS with a known safety profile.

2. **Progressive Multiple Sclerosis (MS).** Approve for 1 year if the patient meets all of the following criteria (A, B and C).
   - A) The patient is ≥ 18 years of age; AND
   - B) Ocrevus is prescribed by, or in consultation with, a physician who specializes in the treatment of MS and/or a neurologist.; AND
   - C) Site of care medical necessity is met*

   Ocrevus is indicated for the treatment of adult patients with relapsing or primary progressive forms of multiple sclerosis.[1] No other disease-modifying MS medications are indicated for use in primary progressive MS.

3. Patient has been Established on Ocrevus. Approve for 1 year if the patient has been taking Ocrevus AND has had a beneficial response to therapy AND Site of care medical necessity is met*

Dosing: IV: 300 mg on day 1, followed by 300 mg 2 weeks later; subsequent doses of 600 mg are administered once every 6 months (beginning 6 months after the first 300 mg dose)

Duration of Therapy is indefinite or until toxicity occurs.

Labs/Diagnostics. Hepatitis B virus screening is required before the first dose.

Waste Management for All Indications.
Injection: 300 mg/10 mL (30 mg/mL) in a single-dose vial.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Ocrevus has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below.

1. **Current Use of Ocrevus with Other Disease-Modifying Agents Used for Multiple Sclerosis (MS).** Ocrevus should not be given in combination with other disease-modifying agents used for MS (e.g., Avonex, Betaseron, Extavia, Rebif, Plegridy, Copaxone, Glatopa, Gilenya, Aubagio, Tecfidera, Tysabri, or Lemtrada). Ocrevus is not indicated for use in combination with other MS disease-modifying therapies and the safety and efficacy have not been adequately established.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

***MMO Site of Care Medical Necessity Criteria:**

- Medications in this policy will be administered in a place of service that identifies the location to be a non-hospital facility based location (i.e., home infusion provider, provider's office, free-standing ambulatory infusion center) unless *at least one* of the following are met[†]:

    1. Age less than 21 years; or
    2. Clinically unstable based upon documented medical history (e.g., patient is hemodynamically unstable); or
    3. History of a severe adverse event from previous administration of the prescribed medication; or
    4. Requested medication is being administered as follows:
        - part of a chemotherapy regimen (e.g., anti-neoplastic agent, colony stimulating factor, erythropoiesis-stimulating agent, anti-emetic) for treatment of cancer; or
        - administered with dialysis; or
    5. Physical or cognitive impairment and caregiver is not available to assist with safe administration of prescribed medication in the home; or
    6. Up to 2 doses of medication or re-initiation after at least 12 months; or
    7. Experiencing adverse events that are not managed by premedication or resources available at a non-hospital facility based location.

[†]This criterion does not apply to Medicare or Medicare Advantage members.

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

Prior approval is required for HCPCS Codes J2350

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HCPCS Code(s):	
J2350	Injection, ocrelizumab, 1 mg (Ocrevus) (Effective date 1/1/2018)