Clinical Criteria

Subject:	Ocrevus (ocrelizumab)		
Document #:	ING-CC-0011	**Publish Date:**	~~06/10/2019~~09/23/2019
Status:	Revised	**Last Review Date:**	~~03/18/2019~~08/16/2019

Table of Contents

Overview
Coding
References
Clinical criteria
Document history

Overview

This document addresses the use of Ocrevus (ocrelizumab), an infused disease modifying therapy approved by the Food and Drug Administration (FDA) to treat primary progressive multiple sclerosis in adults and relapsing multiple sclerosis in adults, including clinically isolated syndrome, relapsing-remitting disease and active secondary progressive disease.

Multiple sclerosis is an autoimmune inflammatory demyelinating disease of the central nervous system. Common symptoms of the disease include fatigue, numbness, coordination and balance problems, bowel and bladder dysfunction, emotional and cognitive changes, spasticity, vision problems, dizziness, sexual dysfunction and pain. Multiple sclerosis can be subdivided into four phenotypes: clinically isolated syndrome (CIS), relapsing remitting (RRMS), primary progressive (PPMS) and secondary progressive (SPMS). Relapsing multiple sclerosis (RMS) is a general term for all relapsing forms of multiple sclerosis including CIS, RRMS and active SPMS.

The treatment goal for multiple sclerosis is to prevent relapses and progressive worsening of the disease. Currently available disease-modifying therapies (DMT) are most effective for the relapsing-remitting form of multiple sclerosis and less effective for secondary progressive decline. DMT include injectable agents, infusion therapies and oral agents.

The FDA approval of Ocrevus for relapsing multiple sclerosis (RMS) was based on two identically designed Phase III double-blind, double-dummy randomized controlled trials, OPERA I and II. Approval for primary progressive multiple sclerosis (PPMS) was based on a randomized, double-blind, placebo-control Phase III clinical trial, ORATORIO.

In the OPERA I and II trials, 1656 study participants were randomized 1:1 to receive Ocrevus or interferon beta-1a (IFN β -1a). Notable inclusion criteria included diagnosis of multiple sclerosis according to the revised McDonald criteria, at least two documented clinical attacks within the last two years prior to screening or one clinical attack in the year prior to screening, neurologic stability for at least the past 30 days at baseline and expanded disability status scale (EDSS) score of 0-5.5. Exclusion criteria included diagnosed with PPMS, EDSS score of < 2.1 with a disease duration over 10 years, immunosuppression and active infection. The primary endpoint in the studies was the annualized relapse rate at week 96 (2 years). Secondary endpoints included confirmed disability progression (CDP) at weeks 12 and 24 and the number of new or enhancing T1 and T2 lesions as seen on MRI at weeks 24, 48 and 96. The superior efficacy of Ocrevus in reducing the annualized relapse rate and disability progression was demonstrated and sustained compared to standard of care IFN β -1a at week 96. In both OPERA I and II, the annualized relapse rate was 16% compared to 29% in the subjects treated with IFN β -1a (absolute risk reduction 13%, NNT = 8, 46% relative risk reduction; p<0.001). The secondary endpoint of a reduction in CDP was also met at week 24 (Hazard Ratio [HR]=0.60, p=0.003). Additionally, the secondary endpoints of a reduction in T1 Gd+ lesions and new/enlarging T2 lesions were also significantly reduced in Ocrevus arms (p<0.0001). There was no significant difference detected in the quality of life between the two arms. Overall, in OPERA I and OPERA II, Ocrevus had a similar safety profile compared with IFN β-1a over 96 weeks.

ORATORIO evaluated the efficacy and safety of Ocrevus (n=488) compared to placebo (n=244) in 732 individuals diagnosed with PPMS who were randomized 2:1. The primary outcome of interest was time to onset of sustained disability progression, defined as an increase in EDSS score that is sustained for at least 12 weeks. Secondary outcomes included interim analysis of the primary outcome at 24 weeks, change in 25-foot walk test from baseline to 120 weeks, and change in volume of T2 brain lesions on MRI. Inclusion criteria included a diagnosis of PPMS as defined by the McDonald criteria and EDSS score of 3 to 6.5. Those with a history of relapsing forms of MS or secondary progressive MS (SPMS) were excluded as were those with other neurologic disorders, active infection, previous treatment with B-cell targeted therapies or lymphocyte trafficking blockers and comorbidities that may require chronic immunosuppressive therapy. The study's primary endpoint was met. A total of 32.9% of subjects in the Ocrevus arm experienced

disability progression lasting 12 weeks or longer compared to 39.3% of subjects in the placebo arm (absolute risk reduction, 6.4%; NNT = 16; HR=0.76, 95% Confidence Interval [CI], 0.59-0.98; p=0.03). A total of 29.6% of Ocrevus subjects experienced disability lasting 24 weeks or longer compared to 35.7% of the subjects receiving placebo injections (absolute risk reduction 6.1%, NNT=17, HR=0.75, 95% CI, 0.58-0.98; p=0.04). At week 120, 402 individuals (82%) in the Ocrevus group and 174 individuals (71%) in the placebo group were available for analysis. There was a statistically significant reduction in the progression rate of 25-foot walk time from baseline to week 120 (55.1% change from baseline in placebo and 38.9% change from baseline in the Ocrevus arm, absolute risk reduction 16.2%, relative risk reduction=29.3% [95% CI, -1.6 to 51.5), p=0.04). The secondary endpoints of reduction in T2 brain lesion volume (mean percent change -3.4 vs +7.4; p<0.0001) as well as the rate of whole brain volume loss (-0.90 vs. -1.09; p=0.02) also favored Ocrevus over placebo at week 120. The mean treatment duration was approximately 3 years, during which time the proportion of study participants experiencing AEs and serious AEs associated with Ocrevus, was similar to placebo. The most serious events were mild-to-moderate infusion-related reactions. A notable potential safety concern was that 2.3% of the Ocrevus arm (n=11; 4 breast cancer, 3 basal cell carcinoma, and 1 each of endometrial adenocarcinoma, anaplastic large cell lymphoma, malignant fibrous histiocytoma, and pancreatic carcinoma) were diagnosed with a malignant neoplasm while only 0.8% (n=2) of the placebo arm were diagnosed with a malignant neoplasm.

The American Academy of Neurology (AAN) guidelines suggest starting disease-modifying therapy in individuals with relapsing forms of multiple sclerosis with recent clinical relapses or MRI activity. The guideline does not recommend one DMT over another. The AAN guidelines also state Ocrevus is the only DMT shown to alter disease progression in individuals with primary progressive multiple sclerosis who are ambulatory and provides a recommendation for Ocrevus for this population.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Ocrevus (ocrelizumab)

Requests for Ocrevus (ocrelizumab) may be approved if the following criteria are met:

I. Individual has a diagnosis of primary progressive multiple sclerosis (PPMS); **AND**
II. Individual is able to ambulate more than 5 meters (not considered wheelchair bound);

OR

III. Individual has a diagnosis of relapsing multiple sclerosis (RMS) (including clinically isolated syndrome, relapsing-remitting disease or active secondary progressive disease); **AND**
IV. Individual is able to ambulate without aid or rest for at least 100 meters; **AND**
V. If initiating therapy, ~~I~~individuals has experienced at least two relapses within the previous two years or one relapse within the previous year.

Ocrevus (ocrelizumab) may not be approved for the following:

I. All other indications not included above; **OR**
~~I.~~II. Individual has active hepatitis B or hepatitis C virus infection or another active infection at initiation of therapy; **OR**
~~II.~~III. Individual has a history of life-threatening infusion reaction to Ocrevus; **OR**
~~III.~~IV. Individual is using to treat non-active secondary progressive multiple sclerosis; **OR**
~~IV.~~V. Individual is using to treat systemic lupus erythematosus; **OR**
~~V.~~VI. Individual is using to treat rheumatoid arthritis; **OR**
~~VI.~~VII. Concurrent use with other MS disease modifying agents (~~such as~~including Aubagio, Avonex, Betaseron, Copaxone/Glatiramer/Glatopa, Extavia, Gilenya, Lemtrada, Mavenclad, Mayzent, Plegridy, Rebif, Tecfidera and Tysabri).

Formatted: Font: Bold

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J2350	Injection, ocrelizumab, 1 mg [Ocrevus]

ICD-10 Diagnosis

G35	Multiple sclerosis

Document History

Revised: 08/16/2019
Document History:

- 08/16/2019 – Annual Review: Update criteria to align with updated labeled indication. Wording and formatting changes. Coding Reviewed: No changes
- 03/18/2019 – Selected Review: Wording and formatting changes. Coding Reviewed: No changes.
- 08/17/2018 – Annual Review: Initial review of ING-CC-0011 Ocrevus (ocrelizumab). Removed diagnostic confirmation and age criteria for consistency with criteria for other MS agents. Updated exclusion for active hepatitis B/C to also exclude if any other active infection is present. Added exclusion for concurrent use with another MS agent. Added new quantity limit.

References

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: July 22, 2019.
2. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
3. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2019; Updated periodically.
4. Olek MJ, Howard J. Clinical presentation, course and prognosis of multiple sclerosis in adults. Last updated: June 11, 2019. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed: July 20, 2019.
5. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018; 90: 777-788. Available from https://www.aan.com/Guidelines/home/GuidelineDetail/898. Accessed: July 20, 2019.
6. Tarver, M. Kurtzke Expanded Disability Status Scale (EDSS). Department of Veterans Affairs: Multiple Sclerosis Centers for Excellence. Last updated: August 3, 2018. Available at: http://www.va.gov/MS/Professionals/Diagnosis/Kurtzke_Expanded_Disability_Status_Scale.asp. Accessed: August 19, 2019.