Department:	Pharmacy Management	**Original Approval:**	06/22/2017
Policy #:	PM142	**Last Approval:**	06/14/2018
Title:	Ocrelizumab (Ocrevus™) injection for intravenous use		
Approved By:	UM Committee		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW

Documentation required to determine medical necessity for Ocrelizumab (Ocrevus) for intravenous use: History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis -Age -Prescribed by or in consultation with a neurologist or specialist.

BACKGROUND

Ocrevus is a CD20-directed cytolytic antibody indicated for the treatment of adult patients with relapsing or primary progressive forms of multiple sclerosis (MS).[1] Ocrevus is given by intravenous (IV) infusion. The initial dose is 300 mg, followed 2 weeks later by a second 300 mg IV infusion. Subsequent doses are 600 mg by IV infusion once every 6 months. Premedicate patients with methylprednisolone (or equivalent corticosteroid) and an antihistamine (e.g., diphenhydramine) prior to each infusion. Patients should be observed for at least 1 hour after infusion completion. Ocrevus should be administered under close supervision of an experienced healthcare professional with accessed to appropriate medical support to manage severe reactions such as serious infusion reactions.

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 Expanded Disability Status Scale (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.

Clinical Efficacy

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.[1-2] Approximately 25% of patients had previously used MS disease-modifying therapy (mainly beta interferon or glatiramer acetate products) within the previous 2 years. In these two trials (OPERA I [n = 821] and OPERA II [n = 835]) 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 < 0.0001).[1-2] In a pooled analysis the proportion of patients with 12-week confirmed disability progression was 9.8% for Ocrevus vs. 15.2% for Rebif, representing a 40% risk reduction (P = 0.0006).[1] Several magnetic resonance imaging (MRI) parameters were also more favorable with Ocrevus vs.

Rebif (e.g., mean number of T1 gadolinium-enhancing lesions per MRI [relative reduction 94.5% [P < 0.0001]).[2]

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]).[1,3] 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 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.[1-2] At baseline, the mean patient age was 45 years, the time since MS symptom onset was 6.7 years, and the mean EDSS score was 4.7.[1] The percentage of patients with primary progressive MS with 12-week confirmed disability progression was 32.9% with Ocrevus vs. 39.3% with placebo representing a 24% risk reduction (P = 0.0321).[1,3] The proprotion of patients with 30% worsening of the timed 25-foot walk confirmed at 12 weeks was 49% in patients given Ocrevus compared with 59% in placebo-treated patients, representing a 25% risk reduction.[1] More favorable MRI results on several parameters were also observed with Ocrevus compared with placebo.[1,3] For example, the mean change in volume of T2 lesions from baseline to Week 120 was superior for Ocrevus compared with placebo (-0.39 cm^3 vs. 0.79 cm^3; P < 0.0001).[1]

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[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] Among the beta interferon products for MS, data suggests Rebif is the most potent. 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® (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]. However, clear benefits have not been definitively established.

DEFINITIONS

None.

INDICATIONS/CRITERIA

MediCAID Members	***Ocrevus is not considered for approval for Relapsing Forms of Multiple Sclerosis unless member has tried and failed 2 preferred products, including: Avonex, Betaseron, Copaxone, Gilenya, Rebif, Tecfidera. Ocrevus is included in the WA HCA Single Preferred Drug List.*** *Document if member meets this criteria, which medications were tried, and deny if criteria is not met. Otherwise, continue to clinical criteria below.*
MediCARE Members	***Continue to criteria for approval below.*** ***Step-utilization of Part D drugs not required***

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, and D):
   - 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) Ocrevus is prescribed by, or in consultation with, a physician who specializes in the treatment of MS and/or a neurologist; AND

D) The patient is negative for HBV infection.

Ocrevus is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis. In the OPERA I and OPERA II trials1-2 Ocrevus significantly lowered the ARR and the proportion of patients with disability progression confirmed at 12 weeks after onset compared with Rebif.[1] Several MRI also demonstrated superiority for Ocrevus vs. Rebif.

2. **Primary 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) The patient is negative for HBV infection

Ocrevus is indicated for the treatment of adult patients with primary progressive forms of MS. [1] In the ORATORIO study, the time to onset of disability progression confirmed at 12 weeks after onset was significantly longer for patients who received Ocrevus compared with placebo-treated patients.[1,3] No other disease-modifying MS medications are indicated for use in primary progressive MS.

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.

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, Lemtrada). The concomitant use of Ocrevus with other immune-modulating or immunosuppressive therapies is anticipated to increase the risk of immunosuppression.[1] Ocrevus is not indicated for use in combination with other MS disease-modifying therapies and the safety and efficacy have not been adequately established. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

SPECIAL CONSIDERATIONS

Contraindications: Ocrevus is contraindicated in patients with active hepatitis B virus infection and/or in patients with a history of life threatening infusion reaction to Ocrevus.

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH PROGRAM	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

CFR		
WAC	WAC 284-43-2050	
RCW		
Contract Citation	☒ WAH	
	☒ IMC	
	☒ MA	
Other Requirements		
NCQA Elements		

1. Ocrevus™ injection for intravenous infusion [prescribing information]. San Francisco, CA: Genentech, Inc (a Member of the Roche Group); March 2017.
2. Hauser SL, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med 2017; 376:221-234.
3. Montelban X, et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. N Engl J Med 2017; 376:209-220."
4. Clinical bulletin. Information for health professionals. Overview of multiple sclerosis. Rosalind Kalb and Nancy Reitman. © 2012 National Multiple Sclerosis Society. Available at: http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Clinical_Bulletin_Overview-of-Multiple-Sclerosis.pdf. Accessed on March 7, 2017.
5. Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis: principles and current evidence. July 2014. Available at: http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/DMT_Consen sus_MS_Coalition.pdf. Accessed on March 7, 2017.
6. Gajofatto A, Turatti M, Benedetti MD. Primary progressive multiple sclerosis: current therapeutic strategies and future perspectives. *Expert Rev Neurother*. 2016 Nov 15:1-14. [Epub ahead of print].
7. Avonex® for intramuscular injection [prescribing information]. Cambridge, MA: Biogen Idec; March 2016.
8. Rebif® for subcutaneous injection [prescribing information]. Rockland, MA: EMD Serono; November 2015.
9. Betaseron® injection for subcutaneous use [prescribing information]. Whippany, NJ: Bayer; April 2016.

10. Extavia® injection for subcutaneous use [prescribing information]. East Hanover, NJ: Novartis; May 2016.
11. Plegridy™ for subcutaneous injection [prescribing information]. Cambridge, MA: Biogen, Inc.; July 2016.
12. Copaxone® injection for subcutaneous use [prescribing information]. Overland Park, KS: Teva Neuroscience; January 2014.
13. Glatopa™ injection for subcutaneous use [prescribing information]. Princeton, NJ: Sandoz, Inc.; January 2014.
14. McGraw CA, Lublin FD. Interferon beta and glatiramer acetate therapy. *Neurotherapeutics*. 2013;10:2- 18.
15. Aubagio® tablets [prescribing information]. Cambridge, MA: Genzyme (a Sanofi Corporation); October 2014.
16. Gilenya® capsules [prescribing information]. East Hanover, NJ: Novartis; February 2016.
17. Tecfidera® delayed-release capsules [prescribing information]. Cambridge, MA: Biogen Idec; February 2016.
18. Tysabri® injection for intravenous use [prescribing information]. Cambridge, MA: Biogen; May 2016.
19. Lemtrada® injection for intravenous use [prescribing information]. Cambridge, MA: Genzyme; July 2016.
20. Mitoxantrone injection [prescribing information]. Irvine, CA: Teva Parenteral Medicines, Inc.; May 2012.
21. Zinbryta™ injection for subcutaneous use [prescribing information]. Cambridge, MA and North Chicago, IL: Biogen and AbbVie; May 2016.
22. Hawker K, O'Connor P, Freedman MS, for the OLYMPUS trial group. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized, double-blind, placebo-controlled multicenter trial. *Ann Neurol*. 2009;66(4):460-471.
23. Wolinsky JS, Narayana PA, O'Connor P, et al, and the PROMiSe Trial Study Group. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo- controlled trial. *Ann Neurol*. 2007;61:14-24.
24. Lublin F, Miller DH, Freedman MS, et al, on behalf of the INFORMS Study Investigators. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomized, double-blind, placebo- controlled trial. *Lancet*. 2016;387:1075-1084.

Other References:

- Calabresi PA.B-Cell Depletion A Frontier in Monoclonal Antibodies for Multiple Sclerosis. N Engl J Med 2017; 376:280-282

Revision History

Revision Date	Revision Description	Revision Made By
06/19/2017	NEW	Sophia Yun, PharmD
06/20/2017	Revisions to reference and special consideration sections per Advanced Medical Records review of clinical guideline	Sophia Yun, PharmD
06/20/2017	Approved	LuAnn Chen, MD, MHA
06/22/2017	Approved	MMLT
03/09/2018	Reassigned from UM164 to PM 142	Cindy Bush
04/13/2018	Moved to new template	Cindy Bush
05/18/2018	Added HBV screening, LOB box	Gary Deng, Pharmacy Student

		Catherine Vu, PharmD
06/14/2018	Approval	UM Committee