



Drug and Biologic Coverage Policy

Effective Date..... 7/1/2020

Next Review Date..... 7/1/2021

Coverage Policy Number 2022

Ozanimod

Table of Contents

Coverage Policy.....	1
FDA Approved Indications	2
Recommended Dosing	2
General Background.....	2
Coding/Billing Information.....	4
References	4

Related Coverage Resources

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Ozanimod (Zeposia®) is considered medically necessary when the following criteria are met:

- Treatment of ONE of the following:
 - Active Secondary Progressive Multiple Sclerosis (SPMS) (for example, SPMS with a documented relapse)
 - Clinically Isolated Syndrome
 - Relapsing-Remitting Multiple Sclerosis

Initial and reauthorization is up to 12 months.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Ozanimod (Zeposia) is considered experimental, investigational or unproven for ANY other use including the following:

- Concurrent use with other disease-modifying agents used for Multiple Sclerosis (for example, Aubagio, Avonex, Betaseron, Copaxone, Extavia, Gilenya, Glatiramer acetate (by Mylan), Glatopa, Lemtrada, Mavenclad, Mayzent, Ocrevus, Plegridy, Rebif, Tecfidera, Tysabri, Vumerity, and Zeposia)

- Non-Relapsing Forms of Multiple Sclerosis (for example, primary progressive multiple sclerosis)

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

FDA Approved Indications

FDA Approved Indication

Zeposia is a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

Recommended Dosing

FDA Recommended Dosing

***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.*

Treatment Initiation

Initiate Zeposia with a 7-day titration, as shown in the table below.

Days 1-4	0.23 mg once daily
Days 5-7	0.46 mg once daily
Day 8 and thereafter	0.92 mg once daily

Maintenance Dosage

After initial titration (see *Treatment Initiation*), the recommended maintenance dosage of Zeposia is 0.92 mg taken orally once daily starting on Day 8.

General Background

Disease Overview

Multiple Sclerosis (MS) is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US. The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. (MS Coalition, 2019)

Advances in the understanding of the MS disease process, as well as in MRI technology, spurred updated disease course descriptions in 2013, as well as in 2017. The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS. Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability. (Lubin, 2013; MS Coalition, 2019; Thompson, 2018)

Professional Societies/Organizations

The AAN practice guideline recommendations regarding disease-modifying therapies for adults with Multiple Sclerosis (MS) makes distinct recommendations of situations in which preferences may be considered, some of which are medication-related. Evidence supports higher efficacy of Lemtrada, Tysabri, Gilenya, and Ocrevus compared with previously self-injectable disease-modifying MS therapies. Subgroup analyses from Phase III pivotal trials with Lemtrada, Gilenya, and Tysabri demonstrate a reduction in MS relapses and MRI measures in patients with MS who have highly-active disease. Compared with beta interferon therapy, treatment with these agents led to more favorable outcomes in the cohort of patients with MS who have highly active disease. For patients with highly-active MS, use of Lemtrada, Gilenya, or Tysabri should be considered (Level B). With Aubagio, there may be a risk of teratogenicity from male sperm, which may last for 2 years following treatment cessation if the patient does not receive chelation therapy. Men with MS should be counseled regarding their reproductive plans before initiating Aubagio therapy (Level B). Tysabri has been associated with progressive multifocal leukoencephalopathy (PML). Regarding oral products, there are rare reports of PML with both Gilenya and Tecfidera. Patients who are considering therapy with Tysabri, Gilenya, Ocrevus, and Tecfidera should be informed about the risks of PML. (Rae-Grant, 2018a)

The AAN published a comprehensive systemic review of disease-modifying therapies for adults with MS. Key statements regarding oral disease-modifying MS therapies are cited below. Of note, this guidance was published before the approval of Mayzent and Mavenclad. The following agents are more effective compared with placebo in reducing the risk of MRI-detected new or enlarging T2 lesions: Gilenya, Rebif (high dose), and Tysabri (high confidence). Mavenclad is probably more effective compared with placebo in reducing the risk of new or enlarging T2 lesions detected by MRI (moderate confidence). The following disease-modifying MS agents are probably more effective compared with other agents in reducing the risk of MRI-detected new or enlarging T2 lesions (moderate confidence): Lemtrada (vs. Rebif), Gilenya (vs. Avonex), and Rebif (vs. Avonex). The following disease-modifying MS agents are more effective compared with placebo in reducing the volume or number of MRI-detected T2 lesions (high confidence): Tecfidera, glatiramer, Avonex, mitoxantraone, Tysabri, and Plegridy. The following agents are more effective than placebo in reducing the risk of disability progression in patients with relapsing remitting MS (high confidence): Tecfidera, Gilenya, Avonex, Rebif, mitoxantrone, Tysabri, Plegridy, and Aubagio. Mavenclad is likely more effective compared with placebo in reducing the risk of disability progression in patients with relapsing remitting MS (moderate confidence). Gilenya is possibly no more effective than Avonex in reducing the risk of disability progression over 3 years (low confidence). In patients with clinically isolated syndrome, the following disease-modifying MS therapies are probably more effective than placebo in reducing the proportion of patients converting to MS (moderate confidence): Mavenclad, Avonex, Betaseron, and Aubagio. (Rae-Grant, 2018b)

Cochrane Network Meta-Analysis

In 2015, a network meta-analysis was published by the Cochrane group regarding immunomodulators and immunosuppressants for relapsing remitting MS. The analysis included 39 studies and involved over 25,000 patients. Most studies were short-term with a median duration of 24 months; 24 trials (60%) were placebo-controlled and 15 studies (40%) were direct comparative trials. Regarding a protective effect against recurrence of relapsing in relapsing remitting MS during the first 24 months of treatment, Lemtrada, mitoxantrone, Tysabri and Gilenya outperformed the other medications investigated listed according to the order of effectiveness. The evidence with Gilenya was noted to be of moderate quality. (Tramacere, 2015)

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative

No recommendations are available for Multiple Sclerosis.

Other Covered Uses

AHFS Drug Information 2020 Edition does support any off-label uses for Zeposia.

Compendium and Other Published Studies

1. Non-Relapsing Forms of Multiple Sclerosis (MS). Note: An example of a non-relapsing form of MS is primary progressive MS. The efficacy of Bafiertam has not been established in patients with MS with non-relapsing forms of MS.
2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

Coding/Billing Information

Note: Ozanimod is typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions, therefore, this section is not in use.

References

1. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. Updated September 2019. Available at: https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/DMT_Consensus_MS_Coalition.pdf. Accessed on November 7, 2019.
2. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014; 83:278-286.
3. McEvoy GK, ed. AHFS 2020 Drug Information. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc; 2020.
4. 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* 2018a; 90:777–788. Available at: <https://n.neurology.org/content/neurology/90/17/777.full.pdf>. Accessed on January 29, 2020.
5. Rae-Grant, Day GS, Marrie RA, et al. Comprehensive systematic review 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*. 2018b; 90:789-800. Available at: <https://n.neurology.org/content/neurology/90/17/789.full.pdf>. Accessed on January 29, 2020.
6. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018; 17(2):162-173.
7. Tramacere I, DelGiovane C, SalantiG, et al. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *Cochrane Database of Systematic Reviews*. 2015, Issue 9. Art. No.: CD011381. DOI: 10.1002/14651858.CD011381.pub2.
8. Zeposia® tablets [prescribing information]. Summit, NJ: March 20120.

"Cigna Companies" refers to operating subsidiaries of Cigna Corporation. All products and services are provided exclusively by or through such operating subsidiaries, including Cigna Health and Life Insurance Company, Connecticut General Life Insurance Company, Cigna Behavioral Health, Inc., Cigna Health Management, Inc., QualCare, Inc., and HMO or service company subsidiaries of Cigna Health Corporation. The Cigna name, logo, and other Cigna marks are owned by Cigna Intellectual Property, Inc. © 2020 Cigna.