09-J3000-98

Original Effective Date: 07/01/21

Reviewed: 06/11/25

Revised: 07/15/25

Subject: Ponesimod (Ponvory™) Tablet

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 triad of 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. Although the clinical course of the disease is capricious, 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.

Ponesimod (Ponvory™) is an immunomodulatory agent that is used to reduce the frequency of relapses and delay the accumulation of physical disability in patients with RRMS. Ponesimod exerts its physiologic effects through attachment to the sphingosine 1-phosphate receptor, which is plays a role in immune function regulation. Ponesimod is Food and Drug administration (FDA) approved for the treatment of relapsing forms of MS to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.In a 108-week randomized, active-controlled, double-blind trial in patients with relapsing forms of MS, treatment with ponesimod resulted in a reduction of the annualized relapse rate (ARR) as compared to teriflunomide (ARR, 0.202 for ponesimod, 0.290 teriflunomide; Relative reduction 30.5%, p=0.0003).There was also a reduction in the number of gadolinium (Gd)-enhancing T1 lesions and the number of new or enlarging T2 lesions in patients treated with ponesimod compared to teriflunomide.There was no statistically significant difference in the 3-month and 6-month confirmed disability progression between the active treatment groups.The most common adverse reactions in patients treated with ponesimod included upper respiratory tract infection, hepatic transaminase elevation, and hypertension.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

NOTE: Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, and Zeposia are the preferred brand products for treatment of relapsing forms of multiple sclerosis. The preferred generic products include dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan), and teriflunomide (generic). Dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan, Glatopa), and teriflunomide (generic) do not require prior authorization.

Initiation of ponesimod (Ponvory™) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. The member is diagnosed with **ONE** of the following forms of multiple sclerosis (MS):
    a. Relapsing remitting multiple sclerosis [RRMS]
    b. Active secondary progressive MS [SPMS]
    c. First clinical episode and member has MRI features consistent with MS
2. **ONE** of the following (a,b,or c) – documentation must be submitted:
    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. **BOTH** of the following (i and ii):
        i. **ONE** of the following (1,2,or 3):
            1. The patient has tried and had an inadequate response to dimethyl fumarate (generic), fingolimod (generic), glatiramer acetate (generic by Mylan, Glatopa), **OR** teriflunomide (generic)
            2. 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)

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

ii. **ONE** of the following (1,2,or 3):

1. The patient has tried and had an inadequate response to **ONE** preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia)
2. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to **ONE** preferred brand agent (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia)
3. The patient has a FDA labeled contraindication to ALL preferred brand agents (Avonex, Betaseron, Kesimpta, Mavenclad, Mayzent, Plegridy, Rebif, Zeposia)

3. Ponesimod 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. Ocrelizumab (Ocrevus)
   m. Ofatumumab (Kesimpta)
   n. Ozanimod (Zeposia)
   o. Peg-interferon beta-1a (Plegridy)
   p. Rituximab (Rituxan or biosimilars)
   q. Siponimod (Mayzent)
   r. Teriflunomide (Aubagio)
   s. Ublituximab (Briumvi)
4. The member does not have any of the following:

a. History (within the last 6 months) of myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or NYHA Class III/IV heart failure

b. History or presence of Mobitz Type II second- or third-degree AV block or sick sinus syndrome (unless member has a functioning pacemaker)

c. Moderate or severe hepatic impairment (Child-Pugh class B or C)

5. The dosage does not exceed 20 mg daily

Approval duration: 1 year

Continuation of ponesimod therapy **meets the definition of medical necessity when ALL** of the following criteria are met:

1. Member has demonstrated a beneficial response to therapy for treatment of RRMS, active SPMS, or clinically isolated syndrome
2. Authorization/reauthorization for ponesimod 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
3. Ponesimod will not be 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. Ocrelizumab (Ocrevus)
    m. Ofatumumab (Kesimpta)
    n. Ozanimod (Zeposia)
    o. Peg-interferon beta-1a (Plegridy)
    p. Rituximab (Rituxan or biosimilars)
    q. Siponimod (Mayzent)

r. Teriflunomide (Aubagio)

s. Ublituximab (Briumvi)

4. The dose does not exceed 20 mg daily

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

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.

Treatment Initiation

The following assessments must be completed prior to treatment:complete blood count, electrocardiogram (ECG) and cardiologist evaluation for certain preexisting conditions, liver function test, ophthalmic evaluation, current or prior medications with immune system effects or cardiovascular conduction effects, and varicella zoster virus antibody testing.

A starter pack must be used for patients initiating treatment.Initiate treatment with a14-day titration; start with one 2 mg tablet orally once daily and progress with the titration schedule as below:

Table 1: Dose Titration Regimen

Titration Day Daily Dose	Mg
Days 1 and 2	2 mg
Days 3 and 4	3 mg
Days 5 and 6	4 mg
Day 7	5 mg
Day 8	6 mg
Day 9	7 mg
Day 10	8 mg
Day 11	9 mg
Days 12, 13, and 14	10 mg

Maintenance Daily Dose

Day 15 and thereafter: 20 mg

If dose titration is interrupted, missed dose instructions must be followed.

Dose Adjustments

- Advice from a cardiologist should be sought to determine the most appropriate monitoring strategy (which may include overnight monitoring) during treatment initiation, if treatment is considered in

patients with some preexisting heart and cerebrovascular conditions, with a prolonged QTc interval before dosing or during the 4-hour observation, or at additional risk for QT prolongation, or on concurrent therapy with QT prolonging drugs with a known risk of torsades de pointes, receiving concurrent therapy with drugs that slow heart rate or AV conduction

- Hepatic Impairment: use is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh class B and C)

Drug Availability

- Tablets: 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, and 20 mg

PRECAUTIONS:

Boxed Warning – none

Contraindications

- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III/IV heart failure
- Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker

Precautions/Warnings

- Infections: may increase the risk of infections. Obtain a complete blood count (CBC) before initiating treatment. Monitor for infection during treatment and for 1-2 weeks after discontinuation. Do not start treatment in patients with active infection.
- Bradyarrhythmia and Atrioventricular Conduction Delays: use may result in a transient decrease in heart rate; titration is required for treatment initiation.Check an electrocardiogram (ECG) to assess for preexisting cardiac conduction abnormalities before starting treatment. Consider cardiology consultation for conduction abnormalities or concomitant use with other drugs that decrease heart rate.
- Respiratory Effects: May cause a decline in pulmonary function. Assess pulmonary function (e.g., spirometry) if clinically indicated.
- Liver Injury: Discontinue if significant liver injury is confirmed. Obtain liver function tests before initiating treatment.
- Increased Blood Pressure (BP): Monitor BP during treatment.
- Cutaneous Malignancies: Skin examination prior to treatment and periodically is recommended.
- Fetal Risk: Women of childbearing potential should use effective contraception during and for 1 week after stopping treatment.
- Macular Edema: An ophthalmic evaluation is recommended before starting treatment and if there is any change in vision while taking ponesimod. Diabetes mellitus and uveitis increase the risk.
- Progressive multifocal leukoencephalopathy (PML): withhold at the first sign or symptom suggestive of PML. Immune reconstitution inflammatory syndrome (IRIS) has been reported in patients treated

with fingolimod who developed PML and subsequently discontinued treatment. IRIS presents as a clinical decline in the patient's condition that may be rapid, can lead to serious neurological complications or death, and is often associated with characteristic changes on MRI. Monitor for development of IRIS.

- Severe Increase in disability after stopping: severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation. After stopping in the setting of PML, monitor for development of immune reconstitution inflammatory syndrome (PML-IRIS).
- Immune system effects: the half-life and mode of action should be considered when switching from drugs with prolonged immune effects to avoid additive effects on the immune system. Ponesimod remains in the blood for up to 1 week, and pharmacodynamic effects may persist for 1 to 2 weeks after the last dose.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, nonchemotherapeutic, NOS

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 last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request

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.

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

Ocrelizumab (Ocrevus), 09-J2000-78

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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2. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2025-May-25].
3. National Multiple Sclerosis Society. Available at http://www.nationalmssociety.org Accessed 04/26/21.
4. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2022 [cited 2022-09-02]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
5. Ponvory (Ponesimod) [package insert]. Janssen Pharmaceuticals, Inc.Titusville, NJ; October 2024.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 06/11/25.

GUIDELINE UPDATE INFORMATION:

07/01/21	New Medical Coverage Guideline.
10/15/22	Review and revision to guideline consisting of updating documentation requirement under initiation criteria and updating list of agents not to be used in combination.
01/01/23	Review and revision to guideline; consisting of updating the position statement to include generic fingolimod as a preferred generic and removal of Gilenya as a preferred brand.
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 and updated warnings.
07/15/25	Review and revision to guideline; consisting of updating the warnings and references.