

09-J1000-82

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Subject: Teriflunomide (Aubagio®) 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.

[Dosage/
Administration](#)

[Position
Statement](#)

[Billing/Coding](#)

[Reimbursement](#)

[Program
Exceptions](#)

[Definitions](#)

[Related
Guidelines](#)

[Other](#)

[References](#)

[Updates](#)

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.

Teriflunomide inhibits the function of specific immune cells that have been implicated in MS and is structurally related to leflunomide (Arava®), an agent used in the treatment of rheumatoid arthritis. Although the exact mechanism by which teriflunomide exerts its therapeutic effects in MS is unknown, it is hypothesized that its presumed immunomodulatory effects are the result of reversible binding to dihydro-orotate-dehydrogenase (DHO-DH) and subsequent inhibition of pyrimidine synthesis in rapidly dividing cells such as T and B lymphocytes. Teriflunomide has been FDA approved for the treatment of individuals with relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults.

In 2018, the American Academy of Neurology published a practice guideline on the use of disease-modifying therapy for adults with multiple sclerosis which includes an assessment of the effectiveness

and safety of teriflunomide in the treatment of MS. Teriflunomide has demonstrated a reduction in measures of disease activity including clinical relapse rate, new and enlarging T2 lesions, and disability progression in patients with relapsing MS.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration 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: Aubagio, Avonex, Betaseron, Gilenya, 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) and glatiramer acetate (generic by Mylan).

Initiation of teriflunomide (Aubagio®) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is diagnosed with **ONE** of the following forms of multiple sclerosis (MS):
 - a. Relapsing-remitting MS [RRMS]
 - b. Active secondary-progressive MS [SPMS]
 - c. First clinical episode and member has MRI features consistent with multiple sclerosis (MS)
2. **ONE** of the following (a,b, or c):
 - 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. **ONE** of the following (i, ii, iii, or iv):
 - i. The patient has tried and had an inadequate response to dimethyl fumarate (generic) **OR** glatiramer acetate (generic by Mylan)
 - ii. 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) **OR** glatiramer acetate (generic by Mylan)
 - iii. The patient has a FDA labeled contraindication to both dimethyl fumarate (generic) **AND** glatiramer acetate (generic by Mylan)

- iv. The prescriber has provided information in support of using the requested agent over dimethyl fumarate (generic) AND glatiramer acetate (generic by Mylan)
3. Teriflunomide 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)
 - f. Glatiramer acetate (Copaxone, Glatopa)
 - g. Interferon beta-1a (Avonex, Rebif)
 - h. Interferon beta-1b (Betaseron, Extavia)
 - i. Leflunomide (Arava)
 - j. Mitoxantrone (Novantrone)
 - k. Monomethyl fumarate (Bafiertam)
 - l. Natalizumab (Tysabri)
 - m. Ocrelizumab (Ocrevus)
 - n. Ofatumumab (Kesimpta)
 - o. Ozanimod (Zeposia)
 - p. Peg-interferon beta-1a (Plegridy)
 - q. Rituximab (Rituxan or biosimilars)
 - r. Siponimod (Mayzent)
4. The member does not have severe hepatic impairment (Child-Pugh Class C)
5. The dose does not exceed 14 mg daily

Approval duration: 1 year

Continuation of teriflunomide 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 teriflunomide 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. Teriflunomide 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)

- f. Glatiramer acetate (Copaxone, Glatopa)
 - g. Interferon beta-1a (Avonex, Rebif)
 - h. Interferon beta-1b (Betaseron, Extavia)
 - i. Leflunomide (Arava)
 - j. Mitoxantrone (Novantrone)
 - k. Monomethyl fumarate (Bafiertam)
 - l. Natalizumab (Tysabri)
 - m. Ocrelizumab (Ocrevus)
 - n. Ofatumumab (Kesimpta)
 - o. Ozanimod (Zeposia)
 - p. Peg-interferon beta-1a (Plegridy)
 - q. Rituximab (Rituxan or biosimilars)
 - r. Siponimod (Mayzent)
4. The dose does not exceed 14 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: Teriflunomide is approved for the treatment of members with relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. The recommended dose is 7- or 14 mg orally once daily, with or without food.

Dosage Adjustments:

- **Renal Impairment:** Dosage adjustments for members with mild, moderate, or severe renal impairment are not required.
- **Hepatic Impairment:** Dosage adjustments for members with mild and moderate hepatic impairment are not required. The pharmacokinetics of teriflunomide in severe hepatic impairment have not been evaluated; teriflunomide is contraindicated in members with severe hepatic impairment (see "Precautions").
- **Geriatric Use:** Clinical studies of teriflunomide did not include individuals over the age of 65.
- **Pediatric Use:** Safety and efficacy in pediatrics has not been established.

Monitoring (Refer to "Precautions" section for additional information)

- Obtain transaminase and bilirubin levels within 6 months before initiation and monitor ALT levels at least monthly for 6 months after starting therapy
- CBC: within 6 months before treatment initiation and as necessary

- Screen for latent tuberculosis
- Blood Pressure: before initiation and periodically during treatment
- Exclude pregnancy

Procedure for Accelerated Elimination: Without an accelerated elimination procedure, teriflunomide takes an average of 8 months to reach plasma concentrations less than 0.02 mg/L. Because of individual variation in drug clearance, it may take as long as 2 years. An accelerated elimination procedure can be used at any time after teriflunomide discontinuation. The following procedures are recommended in the manufacturer's labeling.

- Administration of cholestyramine 8 g every 8 hours for 11 days. If this regimen isn't well tolerated, cholestyramine 4 g three times daily can be used
- Administration of 50 g oral activated charcoal powder every 12 hours for 11 days

If either elimination procedure is poorly tolerated, treatment days do not need to be consecutive unless there is a need to lower teriflunomide plasma concentration rapidly.

Drug Availability: Teriflunomide is supplied as 7- and 14 mg film-coated tablets.

PRECAUTIONS:

Boxed Warnings

- **Hepatotoxicity:** Severe liver injury including fatal liver failure has been reported in individuals administered leflunomide. A similar risk would be expected for teriflunomide because recommended doses of teriflunomide and leflunomide result in a similar range of plasma concentrations of teriflunomide.
 - Obtain transaminase and bilirubin levels within 6 months before initiation of teriflunomide and monitor transaminase levels at least monthly for 6 months.
 - If drug induced liver injury is suspected, discontinue teriflunomide and perform accelerated elimination procedure.
- **Risk of Teratogenicity:** Based on animal data, teriflunomide may cause major birth defects if used during pregnancy. Teriflunomide is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during teriflunomide treatment. Use effective contraception in females of reproductive potential during treatment and during an accelerated drug elimination procedure.

Contraindications

- Severe Hepatic Impairment
- Pregnant women or women of childbearing potential not using reliable contraception may cause fetal harm.
- Hypersensitivity to teriflunomide, leflunomide or any of the inactive ingredients.
- Concomitant leflunomide

PRECAUTIONS/WARNINGS

Peripheral Neuropathy: If a member develops symptoms consistent with peripheral neuropathy, evaluate member and consider discontinuing teriflunomide and using accelerated elimination procedure.

Members greater than 60 years of age, with concomitant nephrotoxic medications, and diabetes may be at an increased risk of peripheral neuropathy.

Hypersensitivity and Severe skin reaction: cases of anaphylaxis, angioedema, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. If members administered teriflunomide develop signs and symptoms of severe allergic reaction, SJS or TEN, discontinue teriflunomide and perform an accelerated elimination procedure.

Blood pressure: teriflunomide may affect blood pressure. Blood pressure should be measured at treatment initiation and periodically during treatment. Elevated blood pressure should be appropriately managed during treatment.

Concomitant use with immunosuppressive or immunomodulating therapies: Co-administration with antineoplastic, or immunosuppressive therapies used for the treatment of MS has not been evaluated. Although safety studies in which teriflunomide was concomitantly administered with other immune modulating therapies for up to one year (interferon beta, glatiramer acetate) did not reveal any specific safety concerns, the long term safety of these combinations has not been established.

Bone marrow effects: A decrease in white blood cell (WBC) count may occur in members treated with teriflunomide. In clinical trials, the decrease in WBC count occurred during the first 6 weeks and the count remained low during treatment. Although no cases of serious pancytopenia were reported in premarketing trials of teriflunomide, rare cases of pancytopenia, agranulocytosis, and thrombocytopenia have been reported in the postmarketing setting with leflunomide. Obtain a complete blood count (CBC) within 6 months before the initiation of teriflunomide treatment. Additional monitoring should be based on signs and symptoms suggestive of bone marrow suppression.

Risk of Infection: teriflunomide should not be initiated in members with active acute or chronic infections until the infection is resolved. If a member develops serious infection while taking teriflunomide, consider suspending treatment and using an accelerated elimination procedure.

Respiratory effects: Interstitial lung disease, including acute interstitial pneumonitis has been reported.

Tuberculosis screening: members should be screened for latent tuberculosis infection with a tuberculin skin test prior to initiating teriflunomide. The safety of teriflunomide in individuals with a positive tuberculin skin test is unknown.

Pregnancy and Lactation

- Teriflunomide is contraindicated in pregnancy and women of childbearing potential who are not using reliable contraception. Teratogenicity and embryofetal lethality occurred in animal reproduction studies in multiple animal species. Exclude pregnancy prior to treatment in women of childbearing potential. If a woman becomes pregnant, treatment should be discontinued and an accelerated drug elimination procedure should occur.
- Additionally, teriflunomide is detected in human semen. To minimize any possible risk, men not wishing to father a child and their female partners should use reliable contraception. Men wishing to father a child should discontinue use of teriflunomide and undergo an accelerated elimination procedure.
- It is not known if teriflunomide is excreted in human milk; however, it was detected in rat milk following a single oral dose.
- Elimination can be accelerated by administration of cholestyramine or activated charcoal for 11 days.

BILLING/CODING INFORMATION:

HCPCS Coding

J8499	Prescription drug, oral, nonchemotherapeutic, NOS
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ICD-10 Diagnosis Codes That Support Medical Necessity:

G35	Multiple Sclerosis
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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 Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

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.

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 individuals 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 individuals.

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

OTHER:

None applicable.

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the BCBSF Pharmacy Policy Committee on 02/10/21.

GUIDELINE UPDATE INFORMATION:

12/15/12	New Medical Coverage Guideline.
03/15/13	Revision to guideline; consisting of updating the position statement.
10/15/13	Review and revision to guideline; consisting reformatting position statement updating references.
01/01/14	Revision to guideline; consisting of updating position statement.
10/15/14	Review and revision to guideline; consisting of reformatting position statement and updating references.
01/01/15	Revision to guideline; consisting of updating position statement.
10/15/15	Review and revision to guideline; consisting of updating position statement, references.
11/01/15	Revision: ICD-9 Codes deleted.
01/01/17	Review and revision to guideline; consisting of updating position statement, precautions and references.
10/15/17	Review and revision to guideline; consisting of updating position statement and references.
12/15/18	Review and revision to guideline; consisting of updating position statement and references.
11/15/19	Review and revision to guideline; consisting of updating position statement, description and references.
07/01/20	Revision to guideline; consisting of updating the position statement.
10/01/20	Revision to guideline; consisting of updating the position statement.
04/01/21	Review and revision to guideline; consisting of updating the position statement.