Medication Policy Manual | **Policy No:** dru283

Topic: Aubagio®, teriflunomide | **Date of Origin:** November 9, 2012

Committee Approval Date: December 16, 2016 | **Next Review Date:** December 2017

Effective Date: January 1, 2017

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Teriflunomide (Aubagio) is an oral medication used in the treatment of relapsing forms of multiple sclerosis (MS). It helps to reduce the number of clinical exacerbations associated with this condition.

Policy/Criteria

I. Most contracts require prior authorization approval of teriflunomide (Aubagio) prior to coverage. Teriflunomide (Aubagio) may be considered medically necessary when all of the following criteria A, B, and C are met.

A. A definitive diagnosis of a relapsing form of multiple sclerosis (relapsing-remitting or secondary progressive multiple sclerosis) that has been established by a specialist in neurology or multiple sclerosis.

AND

B. Teriflunomide (Aubagio) is prescribed by, or in consultation with, a specialist in neurology or multiple sclerosis.

AND

C. Two of the following therapies were documented in clinical notes to be ineffective, contraindicated, or not tolerated:

Dimethyl fumarate (Tecfidera)
Glatiramer acetate
Interferon beta-1a (Avonex)
Interferon beta-1b (Betaseron)
Peginterferon beta-1a (Plegridy)

Ineffectiveness is defined as meeting at least **two** of the following three criteria (1, 2 or 3) during treatment with one of these agents.

1. The patient continues to have clinical relapses (at least one clinical relapse within the past 12 months).
2. The patient continues to have CNS lesion progression as measured by MRI.
3. The patient continues to have worsening disability. Examples of worsening disability include, but are not limited to, decreased mobility, decreased ability to perform activities of daily living due to disease progression, or an EDSS score >3.5.

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx considers teriflunomide (Aubagio) to be a self-administered medication.

B. When prior authorization is approved, teriflunomide (Aubagio) may be authorized in quantities of up to 30 tablets per month.

C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Teriflunomide (Aubagio) is considered investigational when used concomitantly with other disease-modifying multiple sclerosis therapies (see *Appendix A*).

IV. Teriflunomide (Aubagio) is considered investigational when used for all other conditions, including but not limited to:

A. Clinically isolated syndrome

B. Primary progressive (PPMS) MS

C. Progressive relapsing (PRMS) MS

Position Statement

- Teriflunomide (Aubagio) is used in the treatment of relapsing forms of multiple sclerosis (MS). It helps to decrease the number of clinical exacerbations associated with this condition.
- There is no reliable evidence that teriflunomide (Aubagio) is safer or more effective than other disease-modifying medications used in the treatment of MS. Published clinical trials have directly compared teriflunomide to placebo and interferon beta-1a.
- Serious adverse events, including hepatotoxicity and teratogenicity, have been reported with teriflunomide (Aubagio).
- The safety and effectiveness of teriflunomide (Aubagio) when used in combination with other disease-modifying MS medications has not been established.
- Teriflunomide (Aubagio) has not been studied in progressive forms of MS (primary progressive MS and progressive-relapsing MS).
- Teriflunomide (Aubagio) is approved at doses of 7 mg or 14 mg (one tablet) orally daily. Higher doses have not been shown to be safe and effective.

Clinical Efficacy in Multiple Sclerosis

- Two large, phase III randomized controlled trials studied teriflunomide (Aubagio) in the treatment of subjects with relapsing remitting (RRMS) or secondary progressive (SPMS) MS. [1-3]
  * The trials evaluated once daily doses of teriflunomide 7 mg and 14 mg in subjects with relapsing forms of MS over 108 and 48 weeks.
  * Subjects in these trials were not receiving concomitant treatment with other disease-modifying MS therapies.
  * The primary endpoint for both trials was the annualized relapsed rate (ARR), defined as the number of confirmed relapses per trial participant per year.
  * When compared to placebo, subjects treated with either 7 mg or 14 mg of teriflunomide (Aubagio) had a significant reduction in ARR when compared to placebo. Teriflunomide (Aubagio) 14 mg also produced a statistically significant improvement in disability progression; however results for the 7 mg dose were not statistically significant.

- Two small, phase II randomized controlled trials studied teriflunomide (Aubagio) in the treatment of subjects with relapsing forms of MS. One of these trials evaluated the concomitant use of teriflunomide (Aubagio) with interferon beta. [4,5]
    * The meaningfulness of the evidence from thus trials is uncertain because the primary endpoint was reduction of MRI lesions. Additional longer-term, studies are needed to confirm the benefit of combination therapy on
- One phase 3, rater-blinded trial compared teriflunomide (Aubagio) to interferon beta-1a in 324 patients with relapsing multiple sclerosis. [6]
    * The trial did not demonstrate a significant difference between teriflunomide and interferon beta-1a for the primary composite endpoint of time to failure, defined as the first occurrence of confirmed relapse or permanent treatment discontinuation for any cause.
- Evidence for teriflunomide (Aubagio) in clinically isolated syndrome is limited to one randomized trial. Long-term data from large randomized, controlled trials are needed to adequately assess efficacy and safety of teriflunomide in this population.[7]
- Teriflunomide (Aubagio) has not been studied in patients with progressive forms of multiple sclerosis (primary progressive and progressive-relapsing multiple sclerosis).

  The safety and effectiveness of teriflunomide in combination with other disease-modifying MS therapies have not been adequately studied.

Background on Multiple Sclerosis (MS)

- There are four clinical courses of multiple sclerosis (characterized in Table 1 below). [8]
- Relapsing-remitting multiple sclerosis accounts for up to 85% of cases.

Table 1: Multiple Sclerosis Forms/Clinical Course Definitions [8]	
Relapsing-remitting (RRMS)	Characterized by acute relapses that are followed by some degree of recovery; patients do not develop worsening of disability between relapses. The American Academy of Neurology (AAN) defines RRMS as the first clinical course of MS and is characterized by self-limited attacks of neurologic dysfunction. These attacks develop acutely, evolving over days to weeks. Over the next several weeks to months, most patients experience a recovery of function that is often (but not always) complete. Between attacks the patient is neurologically and symptomatically stable.
Secondary progressive (SPMS)	Defined as sustained progression of physical disability occurring separately from relapses, in patients who previously had RRMS. The AAN defines SPMS as the second clinical course which begins as RRMS, but at some point the attack rate is reduced and the course becomes characterized by a steady deterioration in function unrelated to acute attacks.
Primary progressive (PPMS)	Defined as progression of disability from onset without superimposed relapses. The AAN defines PPMS as the third clinical type characterized by a steady decline in function from the beginning without acute attacks.
Progressive relapsing (PRMS)	Defined as primary progressive patients who develop acute relapses well after disease onset. The AAN defines PRMS as the fourth clinical type which also begins with a progressive course although these patients also experience occasional attacks.

Safety [1]

- Teriflunomide (Aubagio) carries warnings for an increased risk of hepatotoxicity and teratogenicity.
- Other significant adverse reactions of teriflunomide (Aubagio) include immunosuppression (increased risk of infection), peripheral neuropathy, acute renal failure, hyperkalemia, blood pressure changes and worsening of lung function.
- The safety of teriflunomide (Aubagio) when used in combination with other disease-modifying MS medications has not been established.

Guidelines

The National Institute for Health and Clinical Excellence (NICE) developed guidelines to address the use of teriflunomide (Aubagio) in relapsing-remitting multiple sclerosis. [9]

- The evidence review group commented that all placebo-controlled clinical trials were short considering the generally long duration of MS and infrequency of relapses, and therefore may not adequately capture differences in relapse rates.
- Teriflunomide (Aubagio) is clinically effective in reducing relapse rates compared with placebo and may have a beneficial impact on accumulation of disability compared with placebo.
- Based on a mixed treatment comparison, there was no difference in effectiveness between teriflunomide and the beta interferons or glatiramer acetate.

- Teriflunomide (Aubagio) is recommended as an option for treating adults with active RRMS (normally defined as 2 clinically significant relapses in the previous 2 years), only if they do not have highly active or rapidly evolving severe RRMS and the manufacturer provides teriflunomide with the discount agreed in the patient access scheme.

Appendix A: Disease-Modifying Agents Used in the Treatment of Multiple Sclerosis (MS)
Alemtuzumab (Lemtrada®)
Daclizumab (Zinbryta™)
Dimethyl fumarate (Tecfidera®)
Fingolimod (Gilenya®)
Glatiramer acetate (Copaxone®)
Interferon beta-1a (Avonex®, Rebif®)
Interferon beta-1b (Betaseron®, Extavia®)
Mitoxantrone (Novantrone®)
Natalizumab (Tysabri®)
Peginterferon beta-1a (Plegridy®)
Ocrelizumab (Ocrevus®)
Teriflunomide (Aubagio®)

Cross References
Betaseron®/Extavia®, interferon beta-1b, Medication Manual, Policy No. 108
Copaxone®, glatiramer acetate, Medication Manual, Policy No. 412
Gilenya®, fingolimod, Medication Manual, Policy No. 229
Lemtrada®, alemtuzumab, Medication Manual, Policy No. 181
Non-Preferred interferon beta products for MS, Medication Manual, Policy No. 108
Preferred interferon beta products for MS, Medication Manual, Policy No. 000
Ocrevus®, ocrelizumab, Medication Manual, Policy No. 000
Tecfidera®, dimethyl fumarate, Medication Manual, Policy No. 299
Tysabri®, natalizumab, Medication Manual, Policy No. 111
Zinbryta™, daclizumab, Medication Manual, Policy No. 465

Codes	Number	Description
HCPCS	J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified
HCPCS	J2323	Injection, natalizumab, 1 mg
ICD-10	G35	Multiple sclerosis

References

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8. Goodin, DS, Frohman, EM, Garmany, GP, Jr., et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology*. 2002 Jan 22;58(2):169-78. PMID: 11805241
9. National Institute for Health and Clinical Evidence (NICE). NICE technology appraisal guidance 303: Teriflunomide for treatment of highly active relapsing-remitting multiple sclerosis. Issue date: January 2014 (Modified June 2014). [cited 10/6/2014]; Available from: http://www.nice.org.uk/guidance/ta303/resources/guidance-teriflunomide-for-treating-relapsingremitting-multiple-sclerosis-pdf.

Revision Date	Revision Summary
12/16/2016	Revised step therapy requirements
12/11/2015	Revised definition of interferon beta ineffectiveness from “two clinical relapses in the past 12 months” to “one clinical relapse in the past 12 months.”