

**Teriflunomide (Aubagio®)**  
**Drug Review**  
AHFS 92:20, Biologic Response Modifiers

**Final Report**  
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Review prepared by:  
Melissa Archer, PharmD, Clinical Pharmacist  
Gary Oderda, PharmD, MPH, Professor

University of Utah College of Pharmacy  
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## Executive Summary

**Introduction:** Teriflunomide (Aubagio®) is an oral disease-modifying agent indicated in the treatment of relapsing forms of multiple sclerosis (MS). Other disease-modifying agents indicated in the treatment of MS include: fingolimod (Gilenya®), glatiramer (Copaxone®), interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaseron®, Extavia®), mitoxantrone (Novantrone®), and natalizumab (Tysabri®). Treatment guidelines for MS recommend a biologic or interferon agent as first-line therapy, but do not recommend one agent over another. Teriflunomide may also be an effective treatment option. Teriflunomide is a pyrimidine synthesis inhibitor, dose once daily, which is thought to reduce pyrimidine-associated inflammation in patients with MS.

**Clinical Efficacy:** Clinical data evaluating the efficacy of teriflunomide in the treatment of MS are limited. In comparative clinical trials, improvements in lesions seen on an MRI scan are significantly improved with teriflunomide therapy compared to placebo. Some evidence suggests improvement in relapse rate with teriflunomide therapy, as well. Data from follow-up trials indicate sustained efficacy and no increases in adverse events.

*Special Populations:* Teriflunomide is contraindicated in pregnant women or women of childbearing age who are not using reliable contraception. Teriflunomide was not studied in lactating women, children, or adults over 65 years of age.

**Adverse Drug Reactions:** Teriflunomide is contraindicated in pregnancy and in patients with severe hepatic insufficiency. The most common adverse events associated with teriflunomide therapy include headache, alopecia, diarrhea, nausea, neutropenia, and elevated liver enzymes. Serious adverse events associated with teriflunomide therapy include serious dermatologic reactions, severe hyperkalemia, acute renal failure and increased susceptibility to infection. No differences in adverse events were reported between teriflunomide doses (7 mg and 14 mg). Teriflunomide is metabolized primarily by hydrolysis which limits the likelihood of drug interactions.

**Summary:** Teriflunomide is an oral disease-modifying agent indicated in the treatment of multiple sclerosis. Limited clinical evidence suggests teriflunomide in combination with interferon beta is more effective than interferon beta alone. Teriflunomide has numerous adverse effects and several serious adverse effects. Teriflunomide is considered a hazardous agent and appropriate precautions should be taken for handling and disposal of the drug.

## Introduction

Teriflunomide (Aubagio®) is an oral disease-modifying agent indicated in the treatment of relapsing forms of multiple sclerosis. Teriflunomide was approved by the FDA in September 2012 in 7 mg and 14 mg doses and was the second oral disease-modifying medication approved for treatment of multiple sclerosis (MS). The first oral disease-modifying agent approved for the treatment of multiple sclerosis was fingolimod (Gilenya®). Many injectable disease modifying agents are available for the treatment of multiple sclerosis: glatiramer (Copaxone®), interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaseron®, Extavia®), mitoxantrone (Novantrone®), and natalizumab (Tysabri®). Table 1 compares the available disease-modifying agents. This review will focus on the safety and efficacy of teriflunomide in the treatment of relapsing forms of multiple sclerosis.

### *Disease Overview*

Demyelinating diseases are neurological disorders defined by the destruction of central nervous system (CNS) tissue and are typically immune-mediated conditions.<sup>1,2</sup> Multiple sclerosis (MS) is the most common demyelinating disorder and is characterized by inflammation, demyelination, scarring, and neuronal loss.<sup>1,2</sup> Patients with MS can exhibit benign illness to a debilitating disease resulting in significant changes to one's lifestyle.<sup>1,2</sup> Multiple sclerosis affects nearly 400,000 individuals in the United States and 2.5 million individuals worldwide.<sup>3-5</sup> The average estimated lifetime cost of illness from MS is estimated to be \$1.2 million.<sup>3-6</sup> Prevalence is higher in women than men and the disease is usually diagnosed between the ages of 20 and 50 years.<sup>3,4,6</sup>

The cause of multiple sclerosis is not known.<sup>1,2</sup> Both genetic (race and gender) and environmental factors (geographical location, exposure to the sun, birth month) are linked to the disease.<sup>7-9</sup> Immunology also plays a role; MS is thought to be an auto-immune disease mediated by T-cells that compromise the blood brain barrier and allow inflammatory mediators to enter and attack the CNS. Diagnosis of MS is based on clinical symptoms in combination with evidence of lesions on magnetic resonance imaging (MRI). Symptoms vary depending on the location and severity of the CNS lesions and may include sensory loss, optic neuritis, weakness, parasthesias, ataxia, tremor, fatigue, cognitive changes, and bladder dysfunction.<sup>1,2</sup>

Multiple sclerosis (MS) is a chronic disease that can progress intermittently or continuously and is divided into four disease courses: relapsing-remitting multiple sclerosis (RRMS), primary-progressive multiple sclerosis (PPMS), secondary-progressive multiple sclerosis (SPMS), and progressive-relapsing multiple sclerosis (PRMS).<sup>1,2</sup> Relapsing-remitting multiple sclerosis is the most common form of MS and is characterized by exacerbations of neurological dysfunction followed by remissions.<sup>10</sup> RRMS may eventually develop into secondary progressive multiple sclerosis which is characterized by a neurologic deterioration with or without relapses. Primary progressive multiple sclerosis occurs in 10-15% of patients with MS and is characterized by disease progression with some minor improvements and without any exacerbations.<sup>9,11</sup> Progressive relapsing multiple sclerosis affects less than 5% of patients and is characterized by disease progression with acute relapses. Most medications used in the

treatment of MS are indicated in the treatment of RRMS or SPMS; there are currently no medications labeled for use in PPMS.<sup>1,2</sup>

Treatment of MS varies depending on the clinical subset of MS present and individual patient characteristics.<sup>1,2,4,6</sup> In general, treatment may include disease modifying agents in combination with symptomatic treatment.<sup>1,2</sup> Symptomatic treatments include glucocorticoid therapy, benzodiazepines, muscle relaxers, anticonvulsants, antidepressants, and medications used to treat urinary disorders.<sup>1,2</sup> Currently, no curative medication therapies are available in the treatment of MS.<sup>4,6</sup> Disease-modifying agents provide symptomatic relief and reduced disease progression.<sup>24</sup> Many injectable disease-modifying agents are available for use in MS and two oral agents are available. Treatment guidelines for multiple sclerosis cite many of the biologic and interferon agents as effective treatment options, but do not recommend one therapy over another.<sup>12-14</sup> The interferon agents and glatiramer demonstrate reduced relapse rates and slowed disease progression and may be considered first-line therapy in RRMS.<sup>14</sup> Natalizumab and mitoxantrone may be considered in progressive patients who do not respond to or tolerate other disease-modifying therapies.<sup>14</sup> Evidence evaluating teriflunomide, the oral pyrimidine synthesis inhibitor, suggests teriflunomide is safe and effective in reducing acute MS attacks and may be more convenient treatment option for patients.<sup>15</sup>

**Table 1. Comparison of Disease Modifying Agents used in the Treatment of Multiple Sclerosis<sup>15-17</sup>**

Product	Drug class	Administration	Labeled uses	Unlabeled uses	Dosing	Generic Available
<b>Fingolimod (Gilenya)</b>	Sphingosine 1-Phosphate (S1P) Receptor Modulator	Oral; patient self-administered	Treatment of relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and delay disability progression	N/A	0.5mg once daily; doses >0.5mg/day associated with increased adverse events and no additional benefit	No
<b>Glatiramer (Copaxone)</b>	Biological	Subcutaneous; patient self-administered	Management of relapsing-remitting type multiple sclerosis, including patients with a first clinical episode with MRI features consistent with multiple sclerosis	N/A	20mg daily	No
<b>Interferon beta-1a (Avenox)</b>	Interferon	Intramuscular; patient self-administered or in physician's office	Treatment of relapsing forms of multiple sclerosis (MS); clinical isolated syndrome	Treatment of secondary progressive forms of multiple sclerosis (MS); to decrease the number and volume of active brain lesions, decrease overall disease burden, and delay onset of clinically definite MS in patients who have experienced a single demyelinating event.	30mcg weekly	No
<b>Interferon beta-1a (Rebif)</b>	Interferon	Subcutaneous; patient self-administered	Treatment of relapsing forms of multiple sclerosis (MS)	Treatment of secondary progressive forms of multiple sclerosis (MS); clinical isolated syndrome	22-44mcg three times weekly, with gradual dose titration	No
<b>Interferon beta-1b (Betaseron, Extavia)</b>	Interferon	Subcutaneous; patient self-administered	Treatment of relapsing forms of multiple sclerosis (MS); treatment of first clinical episode with MRI features consistent with MS	Treatment of secondary-progressive MS	62.5-250mcg every other day, with gradual dose titration	No
<b>Mitoxantrone (Novantrone)</b>	Anthracenedione antineoplastic agent	Intravenous; in clinic or hospital setting capable of administering chemotherapy	Initial treatment of acute nonlymphocytic leukemias (ANLL [includes myelogenous, promyelocytic, monocytic and erythroid leukemias]); treatment of advanced hormone-refractory prostate cancer; secondary progressive or relapsing-remitting multiple sclerosis (MS)	Treatment of Hodgkin lymphoma (refractory), non-Hodgkin lymphomas (NHL), acute lymphocytic leukemia (ALL), relapsed acute myeloid leukemia (AML), breast cancer (metastatic), pediatric acute myelogenous leukemia (AML), pediatric acute promyelocytic leukemia (APL); part of a conditioning regimen for autologous hematopoietic stem cell transplantation (HSCT), metastatic breast cancer, relapsed leukemia (adults), lymphoma, hepatocellular carcinoma,	12mg/m <sup>2</sup> every 3 months (maximum lifetime cumulative dose: 140 mg/m <sup>2</sup> )	Yes
<b>Natalizumab (Tysabri)</b>	Monoclonal Antibody, Selective Adhesion-Molecule Inhibitor	Intravenous; in clinic or hospital setting	Monotherapy for the treatment of relapsing forms of multiple sclerosis; treatment of moderately- to severely-active Crohn's disease	Combination use with glatiramer or interferon beta for relapsing forms of multiple sclerosis	300mg every 4 weeks	No
<b>Teriflunomide (Aubagio)</b>	Pyrimidine Synthesis Inhibitor	Oral; patient self-administered	Treatment of relapsing forms of multiple sclerosis (MS)	N/A	7 mg or 14 mg once daily	No

## Pharmacology

Teriflunomide is the active metabolite of leflunomide, a disease-modifying agent used in the treatment of rheumatoid arthritis.<sup>1,2,15</sup> Teriflunomide is a pyrimidine synthesis inhibitor which works by inhibiting the activity of dihydro-orotate dehydrogenase (DHODH), the rate-limiting enzyme in the biosynthesis of pyrimidine, and altering its activity in antiproliferative and inflammatory processes.<sup>15</sup> In multiple sclerosis, teriflunomide appears to reduce the number of activated lymphocytes in the central nervous system (CNS) resulting in decreased CNS inflammation.<sup>1,2,15</sup>

## Pharmacokinetics

Teriflunomide is dosed 7 mg or 14 mg once daily with or without food.<sup>15</sup> Clinical trials evaluating leflunomide and teriflunomide report teriflunomide is highly protein bound in plasma (99.3%) and has a low volume of distribution. Teriflunomide is metabolized primarily by hydrolysis to minor metabolites and may inhibit hepatic CYP2C9 isoenzymes.<sup>16,17</sup> Teriflunomide has a half-life of about two weeks, is cleared by hepatic metabolism, and is contraindicated in patients with severe hepatic insufficiency. Teriflunomide does not require dose adjustment in renal insufficiency. Variations in clearance are reported with teriflunomide use and it may take up to 2 years to reach low levels of teriflunomide metabolite serum concentrations.<sup>15</sup>

## Methods

A literature search was conducted to identify articles addressing each key question, searching the MEDLINE database (1950 – 2013), the Cochrane Library, and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE prior to February 2013, evaluating the efficacy of teriflunomide with reduction of symptoms or improvement in disease are included. Trials evaluating teriflunomide as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Trials comparing monotherapy with combination regimens are excluded. The following reports were excluded (note: some were excluded for more than 1 reason):

- Individual clinical trials which evaluated other endpoints, such as pharmacokinetic studies<sup>18-21</sup> or pharmacology studies.<sup>22-24</sup>
- Individual trials comparing teriflunomide in dose-finding studies or in healthy volunteers.<sup>18,25</sup>
- Individual clinical trials without access to the full article.

## Clinical Efficacy

Three clinical trials are available for evaluation of teriflunomide in the treatment of MS.<sup>26-28</sup> Two of the trials are reviewed in a meta-analysis.<sup>29</sup> Several

extension or review articles evaluating the clinical trials are also available.<sup>30, 31</sup> The studies evaluated patients (predominantly adult women) with symptoms and a magnetic resonance imaging (MRI) scan indicative of relapsing multiple sclerosis. Patients with a score of 0-6 out of 10 on the Expanded Disability Status Scale (EDSS; higher scores indicate greater disability) were included. Patients received teriflunomide doses of 7 mg or 14 mg once daily for up to 108 weeks. All trials evaluated the relapse rate, defined as a new or worsening symptom and an increase in EDSS score of 0.5 or more.

He et al<sup>29</sup> performed a meta-analysis to assess the safety and efficacy of teriflunomide in patients with different forms of MS (relapsing-remitting and secondary progressive). They included trials reporting rate of relapse, disability progression, and number of brain lesions as outcomes. Two studies, involving 1204 patients, met the inclusion criteria. The first trial, O'Connor et al 2011<sup>27</sup>, was a large phase III, double-blind, parallel-group study. In this trial, 1088 patients with MS were randomized to receive either teriflunomide 7 mg or 14 mg or placebo for 108 weeks. A significantly reduced relapse rate for both teriflunomide groups (37%) was demonstrated compared to placebo (54%;  $p < 0.001$ ). Significantly fewer lesions per MRI scan were also reported in the teriflunomide-treated groups compared to placebo ( $p < 0.001$ ). The second trial, Freedman et al<sup>28</sup>, was a phase II, multicenter, double-blind study. In this trial, 116 patients with MS already receiving interferon beta therapy were randomized to receive either teriflunomide 7 mg or 14 mg or placebo for 24 weeks. Patients who completed the 24 weeks of treatment could then enter a 24-week extension study. The number of lesions was reduced in both teriflunomide groups compared interferon beta alone at 48 weeks ( $p < 0.005$ ). No significant differences in relapse rate were reported. Because the two studies were of low quality and short duration and were funded by a pharmaceutical company, the meta-analysis did not offer a clear recommendation for teriflunomide use in MS. The most frequent adverse events reported with teriflunomide therapy included headache, diarrhea, fatigue, elevated liver enzymes, nausea, alopecia, influenza, and infection.

A third clinical trial evaluating teriflunomide therapy in MS is available. O'Connor et al 2006<sup>32</sup>, is a phase II, double-blind study. In this trial, 179 patients with MS were randomized to receive either teriflunomide 7 mg or 14 mg or placebo for 36 weeks. Significantly fewer lesions per MRI scan were reported in the teriflunomide treatment groups compared to placebo ( $p < 0.001$ ). No significant differences in relapse rate or adverse event rate were reported between treatment groups. An open-label extension study<sup>30</sup> was available for patients interested in continuing teriflunomide therapy. Patients were followed for up to 8.5 years and monitored for efficacy and adverse events. Throughout the study, relapse rates remained low and a dose-dependent improvement in MRI scan was seen with teriflunomide 14 mg. Treatment-emergent discontinuation rate was 19% at the end of the study period. The most common adverse events reported with treatment were mild infections, fatigue, sensory disturbances and diarrhea.

Clinical data evaluating the efficacy of teriflunomide in the treatment of MS are limited. In comparative clinical trials, improvements in lesions seen on an MRI are

significantly improved with teriflunomide and interferon beta therapy compared to interferon beta therapy alone. In one large trial, relapse rate was also significantly improved at 18 weeks of treatment. One long-term trial reported a dose-dependent improvement in MRI scan with teriflunomide 14 mg. Data from follow-up trials indicate sustained efficacy and no increases in adverse events. Overall, teriflunomide is an efficacious treatment option for patients with relapsing multiple sclerosis.

### *Special Populations*

Evidence evaluating teriflunomide in special populations is limited. A sub group analysis<sup>31</sup> of a clinical trial evaluating teriflunomide therapy in patients with MS reported consistent efficacy in patients with different demographics (gender, race, age), disease characteristics (Expanded Disability Status Scale (EDSS), relapse history, multiple sclerosis (MS) subtype), MRI parameters and prior use of MS drugs. Teriflunomide was not studied in lactating women, children, or adults over 65 years of age.<sup>15</sup> Teriflunomide has a black box warning stating teriflunomide may cause major birth defects if used in pregnant women. Teriflunomide is contraindicated in pregnant women or women of childbearing age who are not using reliable contraception.<sup>15-17</sup>

### **Adverse Drug Reactions**

Teriflunomide is contraindicated in pregnancy and in patients with severe hepatic insufficiency.<sup>15-17</sup> Teriflunomide is considered a hazardous agent and appropriate precautions should be taken for handling and disposal of the drug. The most common adverse events associated with teriflunomide therapy include headache (19-22%), alopecia (10-13%), diarrhea (15-18%), nausea (9-14%), neutropenia (2-15%), and elevated liver enzymes (12-14%). Serious adverse events associated with teriflunomide therapy include serious dermatologic reactions, severe hyperkalemia (>7.0 mmol/L), acute renal failure, and increased susceptibility to infection. Teriflunomide therapy may also be associated with increases in blood pressure and peripheral neuropathy. No differences in adverse events were reported between teriflunomide doses (7 mg and 14 mg). Complete blood count, complete metabolic panel, and other pertinent lab values (creatinine, liver enzymes, etc.) should be monitored within 6 months of initiation and periodically thereafter while receiving treatment.<sup>15-17</sup>

Teriflunomide is metabolized primarily by hydrolysis which limits the likelihood of drug interactions.<sup>15-17</sup> Some evidence suggests teriflunomide may inhibit hepatic CYP2C9 isoenzymes and enhance the anticoagulant effect of warfarin. Coadministration of teriflunomide with other immunosuppressive agents may result in increased immunosuppression. Coadministration of teriflunomide with bile acid sequestrants may decrease the serum concentration of teriflunomide. Although drug interactions may occur, no other significant drug-drug interactions with teriflunomide are known.<sup>15-17</sup>

## Summary

Teriflunomide is a pyrimidine synthesis inhibitor indicated in the treatment of relapsing-remitting multiple sclerosis. It is one of two available oral disease-modifying agents and is dosed once daily. The exact mechanism of action of teriflunomide is not known but it is thought to inhibit the activity of pyrimidine and alter their activity in antiproliferative and inflammatory processes. Treatment guidelines for multiple sclerosis recommend many of the biologic and interferon agents as effective treatment options, but do not recommend one therapy over another. Only placebo-controlled clinical evidence is available for evaluation of teriflunomide in the treatment of MS. Compared to placebo, teriflunomide therapy significantly improved CNS lesions. Some evidence suggests teriflunomide therapy may also improve relapse rates. The most common adverse events reported with teriflunomide therapy include headache, alopecia, diarrhea, nausea, neutropenia, and elevated liver enzymes. The most serious adverse events associated with teriflunomide therapy are serious dermatologic reactions, severe hyperkalemia, acute renal failure, and increased susceptibility to infection. Teriflunomide is considered a hazardous agent and appropriate precautions should be taken for handling and disposal of the drug.

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