# Teriflunomide: A Once-daily Oral Medication for the Treatment of Relapsing Forms of Multiple Sclerosis

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## ABSTRACT

**Purpose:** The purpose was to summarize US prescribing information for teriflunomide in the treatment of patients with relapsing forms of multiple sclerosis (RMS), with reference to clinical efficacy and safety outcomes.

**Methods:** In September 2012, the US Food and Drug Administration granted approval for the use of teriflunomide, 14 mg and 7 mg once daily, to treat RMS on the basis of the results of a Phase II study and the Phase III TEMSO (Teriflunomide Multiple Sclerosis Oral) trial. After recent updates to the prescribing information (October 2014), key findings from these and 2 other Phase III clinical trials, TOWER (Teriflunomide Oral in People With Relapsing Multiple Sclerosis) and TOPIC (Oral Teriflunomide for Patients with a First Clinical Episode Suggestive of Multiple Sclerosis), and practical considerations for physicians are summarized.

**Findings:** Teriflunomide, 14 mg and 7 mg, significantly reduced mean number of unique active lesions on magnetic resonance imaging (MRI; $P < 0.05$ for both doses) in the Phase II study. In the TEMSO and TOWER studies, the 14-mg dose of teriflunomide significantly reduced annualized relapse rate (31% and 36% relative risk reduction compared with placebo, respectively; both $P < 0.001$) and risk of disability progression sustained for 12 weeks (hazard ratio vs placebo 0.70 and 0.69, respectively; both $P < 0.05$). The 7-mg dose significantly ($P < 0.02$) reduced annualized relapse rate in both studies, although the reduction in risk of disability progression was not statistically significant. Teriflunomide treatment was also associated with significant efficacy on MRI measures of disease activity in TEMSO; both doses significantly reduced total lesion volume and number of gadolinium-enhancing T1 lesions. TOPIC evaluated patients with a first clinical event consistent with acute demyelination and brain MRI lesions characteristic of multiple sclerosis. More patients were free of relapse in the teriflunomide 14-mg and 7-mg groups than in the placebo group ($P < 0.05$ for both comparisons). In safety data pooled from the 4 studies, adverse events occurring in $\geq 2\%$ of patients and $\geq 2\%$ higher than in the placebo group were headache, alanine aminotransferase increase, diarrhea, alopecia (hair thinning), nausea, paresthesia, arthralgia, neutropenia, and hypertension. Routine monitoring procedures before and on treatment are recommended to assess potential safety issues. Women of childbearing potential must use effective contraception and, in the event of pregnancy, undergo an accelerated elimination procedure to reduce plasma concentrations of teriflunomide.

**Implications:** Clinical evidence suggests that teriflunomide is an effective therapeutic choice for patients with RMS, both as an initial treatment and as an alternative for patients who may have experienced intolerance or inadequate response to a previous or current disease-modifying therapy. (*Clin Ther.* 2015;37:2366–2380) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

**Key words:** efficacy, multiple sclerosis, oral disease-modifying therapy, safety, teriflunomide.

## INTRODUCTION

Teriflunomide* is a once-daily oral immunomodulator with anti-inflammatory properties, licensed for the treatment of patients with relapsing forms of multiple sclerosis (RMS).[1] Teriflunomide received US Food and Drug Administration (FDA) approval in September 2012

*Trademark: Aubagio® (Genzyme, Cambridge, Massachusetts).

*Accepted for publication August 2, 2015.*
http://dx.doi.org/10.1016/j.clinthera.2015.08.003
0149-2918/$ - see front matter

and was the second oral disease-modifying therapy to be licensed for RMS. Three oral agents are now available, including fingolimod[†,2] and dimethyl fumarate[‡,3] which provide an alternative to the injectable therapies, interferon-β and glatiramer acetate, that have some limitations for tolerability, efficacy, and patient acceptability.

The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but it likely involves a reduction in the number of activated lymphocytes that enter the central nervous system. Teriflunomide selectively and reversibly inhibits dihydroorotate dehydrogenase, a key mitochondrial enzyme in de novo pyrimidine synthesis that is required by rapidly dividing lymphocytes. Blocking dihydroorotate dehydrogenase results in a reversible cytostatic effect that limits the expansion of stimulated T and B cells thought to be responsible for the damaging inflammatory process associated with MS. In contrast, resting and slowly dividing cells, including lymphocytes and nonlymphoid cells, rely on the pyrimidine salvage pathway to meet their pyrimidine demand. Because this pathway is not affected by teriflunomide, basic homeostatic functions of resting and slowly dividing cells appear to be preserved, and immune cells remain available for immune surveillance.[4,5]

Teriflunomide is the active metabolite of leflunomide[§], a drug licensed for the treatment of active rheumatoid arthritis since 1998.[6] The extensive clinical experience with leflunomide (>2.58 million patient-years of cumulative exposure) has informed the teriflunomide US prescribing information about its safety profile. However, note that leflunomide was only evaluated in patients with rheumatoid arthritis, whose condition is often confounded by comorbidities and concomitant medications.

Teriflunomide is approved in >50 countries and, as of August 2014, ~30,000 patients were treated with teriflunomide in clinical trials and postmarketing settings worldwide.

This review summarizes key data that supported FDA approval of teriflunomide, 14 mg and 7 mg, and informed recommendations in the US prescribing information. The prescribing recommendations are also reviewed, with the aim of providing a practical summary for US clinicians who wish to prescribe teriflunomide for patients with RMS.

[†]Trademark: Gilenya® (Novartis, East Hanover, New Jersey).

[‡]Trademark: Tecfidera® (Biogen Idec, Cambridge, Massachusetts).

[§]Trademark: Arava® (sanofi-aventis, Bridgewater, New Jersey).

## KEY FINDINGS FROM CLINICAL TRIALS

The FDA approval of teriflunomide in September 2012 was based primarily on safety and efficacy data from 2 randomized, placebo-controlled clinical trials that evaluated the teriflunomide 14-mg and 7-mg once-daily doses in patients with RMS: the 108-week Phase III TEMSO (Teriflunomide Multiple Sclerosis Oral) study (Study 1; NCT00134563[7]) and a 36-week Phase II study (Study 4; NCT01487096[8]). In October 2014, the teriflunomide prescribing information was updated to include data from 2 additional randomized, placebo-controlled Phase III trials: TOWER (Teriflunomide Oral in People With Relapsing Multiple Sclerosis; Study 2; NCT00751881[9]) in patients with RMS, and TOPIC (Oral Teriflunomide for Patients with a First Clinical Episode Suggestive of Multiple Sclerosis; Study 3; NCT00622700[10]) in patients with a first demyelinating event consistent with MS (Table I).

### Clinical and Magnetic Resonance Imaging Outcomes

#### *Phase II Study*

The 36-week Phase II study of 179 patients with clinically confirmed MS[11] and a history of relapse reported positive outcomes with teriflunomide on magnetic resonance imaging (MRI) variables. The mean number of unique active lesions per scan was significantly lower in the teriflunomide 14-mg and 7-mg groups (0.98 and 1.06 lesions/scan, respectively) than in the placebo group (2.69 lesions/scan; $P = 0.0052$ and $P = 0.0234$, respectively) (Figure 1).[1,8]

#### *TEMSO*

TEMSO[1,7] enrolled 1088 patients with active disease (baseline Expanded Disability Status Scale [EDSS] scores ≤5.5, and at least 2 clinical relapses in the previous 2 years or 1 relapse during the preceding year) who met the McDonald 2001 criteria[12] for MS and had a relapsing clinical course with or without progression. The majority of patients enrolled (91%) had relapsing-remitting MS, with the remainder having a progressive form of MS with relapses. Teriflunomide 14 mg significantly reduced the risk of confirmed disability progression sustained for