

Brand Name^{1,2,3}: Aubagio

Generic Name^{1,2,3}: Teriflunomide

Manufacturer⁴: Genzyme (a Sanofi company)

Drug Class^{1,2}: neurological agents, central nervous system agent, dihydroorotate dehydrogenase inhibitor

Uses

Labeled Uses^{1,2,3}: relapsing forms of multiple sclerosis

Unlabeled Uses^{1,2,3,4}: teriflunomide does not currently have any off-label uses

Mechanism of Action

^{1,2,3,4}:

Teriflunomide is a selective, non-competitive, reversible inhibitor of dihydroorotate dehydrogenase (a mitochondrial enzyme involved in *de novo* pyrimidine synthesis). This causes antiproliferative effects among peripheral T- and B- lymphocytes, lowering the concentration of activated lymphocytes in the CNS and therefore reducing the inflammatory demyelination occurring in multiple sclerosis.

Pharmacokinetics

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Absorption:

T _{max}	1-4 hours
V _d	11L
T _{1/2}	18-19 days
Clearance	30.5mL/hr
Protein (Albumin) Binding	>99%
Bioavailability	100%

Food has no effect on absorption. It may take 3 months of use before steady-state concentration is achieved.

Metabolism: Teriflunomide undergoes primary hydrolysis and oxidation to form minor metabolites, but is found as the principal active moiety in plasma. Secondary metabolism pathways include oxidation, N-acetylation, and sulfate conjugation. It is a CYP1A2 inducer and inhibitor of CYP2C8, BCRP, OATP1B1, and OAT3. Also a substrate of BCRP.

Elimination: Teriflunomide is excreted unchanged through biliary excretion and its metabolites are excreted renally. The median half-life in healthy patients following repeated administration is 18-19 days. Total body clearance is 30.5ml/hr.

Efficacy^{5,6,7}:

⁵O'Connor P., Wolinsky J., Confavreux C., Comi G., Kappos L., Olsson T., et al. (2011b) Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med.* Oct6;365(14): 1293–1303.

Study Design: Phase III, multicenter, double blind, randomized, placebo-controlled study

Description of Study: *Methods:* In this study, 1088 relapsing multiple sclerosis patients from 127 clinical centers across 21 countries were randomized to receive either placebo or teriflunomide, 7 or 14mg once daily for 108 weeks. Patients were between the ages of 18 and 55 years, met the McDonald criteria for MS diagnosis, and exhibited a relapsing clinical course. Patients were randomized 1:1:1 to three once-daily treatment groups. The primary objective of the study was to determine the effect on number of relapses per year. The key secondary objective was to determine the effect of teriflunomide on disability progression as measured from baseline. *Results:* A total of 869 patients completed the study, with similar proportions across the treatment groups. Across the total population, the annualized relapse rate was 54% (95% CI 47%-62%) for patients on placebo, 37% (95% CI 32%-43%) for patients on 7mg teriflunomide, and 37% (95% CI 31%-44%) for patients on 14mg teriflunomide ($p < 0.001$). The probability of disability progression across all patients was 27% (95% CI 22%-32%) in the placebo group, 22% (95% CI 17%-26%) for patients on 7mg teriflunomide, and 20% (95% CI 17%-26%) for patients on 14mg teriflunomide ($p = 0.03$). Both teriflunomide doses were superior to placebo on a range of endpoints measured by MRI.

Limitations: Most of the authors received research support, consulting fees, educational grants, or have served as speakers for the manufacturer of teriflunomide (Sanofi-Aventis). Sanofi-Aventis supported the study. Additionally, the power of the study was not specified, however the sample size for each group seemed adequate. Most of the patients were Caucasian females, making it difficult to extrapolate results to people outside of that demographic.

Conclusion Teriflunomide looks promising for decreasing annual relapse rate among patients with relapsing multiple sclerosis, as well as preventing disability progression in those patients. Further studies could evaluate the safety and efficacy in groups of patients with larger demographic variability at baseline so that results could be further extrapolated.

⁶Confavreux C., Li D., Freedman M., Truffinet P., Benzerdjeb H., Wang D., et al. (2012) Long-term follow-up of a phase 2 study of oral teriflunomide in relapsing multiple sclerosis: safety and efficacy results up to 8.5 years. *Mult Scler.* Sept;18(9): 1278–1289

Study Design Randomized, open-label follow-up of a placebo-controlled phase 2 study.

Description of Study *Methods:* 147 patients who had completed a core study entered an open-label extension. Patients who had been receiving either 7mg or 14mg of oral teriflunomide daily continued their current regimen and those who had been taking placebo were randomly re-allocated to take teriflunomide either 7mg or 14mg daily in a 1:1 fashion. For the core study, patients had to have an Expanded Disability Status Scale (EDSS) of 6 or less and at least two clinical relapses in the previous 3 years and one during the preceding year. The primary endpoint was to assess long-term safety of teriflunomide, while secondary objectives assessed efficacy in terms of

relapse rate, disability accumulation, MRI outcomes, and quality of life. Clinical efficacy outcomes, annualized relapse rate (ARR) and EDSS were assessed every 24 weeks. MRI scans were analyzed every 48 weeks from the beginning of the extension. In accordance with the statistical analysis plan, no formal statistical tests were performed on the efficacy data. The core study began April 26, 2001 and ended March 17, 2003. The arbitrary interim analysis cutoff occurred on January 8, 2010 at which time 62 (42.2% of the patients who had entered the extended study) had discontinued treatment, but only 19% were due to adverse effects. Almost every patient reported at least one adverse event over the study period. These included infections, hepatic disorders, gastrointestinal disorders, neurological disorders, psychiatric disorders, and haematologic abnormalities. *Results:* Annualized relapse rates decreased over the 372-week evaluation in both teriflunomide groups. Patients had minimal disease progression throughout the study period. Also MRI imaging revealed that newly active lesions and enlarging lesions were reduced with teriflunomide during treatment, with the activity lower in the 14mg group. There was also an average increase of 3.8 points on the quality of life FIS scale, which was not considered clinically relevant. Most adverse events were mild to moderate, with only isolated severe adverse effects. No serious opportunistic infections or hypersensitivities were reported, and there were only isolated reports of WBC decreases. The incidence rate of malignancies were within the normal range. Two patients became pregnant during treatment and continued with their pregnancies. They followed a rapid drug elimination procedure and both had healthy babies with no structural defects or functional problems.

Limitations: Only 85 out of the 147 patients remained on treatment at the cutoff date. Funding for the study was provided by Sanofi-Aventis, the owner of the manufacturing company for teriflunomide. Most of the authors received funding from Sanofi-Aventis at some point, possibly causing a conflict of interest. Also, statistical tests were not performed in this study, leaving the question as to whether the results will be statistically significant in the general population. This was an open-label study, leaving to question whether unblinding may have played a role in how patients reported their symptoms.

Conclusion Although safety and efficacy data over the 8.5 year trial look promising, more studies with a larger sample size will need to be done to accurately assess long-term treatment with teriflunomide, especially from a statistical standpoint.

⁷O'Connor P., Li D., Freedman M., Bar-Or A., Rice G., Confavreux C., et al. (2006) A phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. *Neurology*66: 894–900.

Study Design Randomized, double-blind, placebo-controlled, Phase II study

Description of Study Methods: In this study, 179 patients with either relapsing-remitting MS (157/179) or secondary progressive MS with relapses (22/179) were randomized 1:1:1 to receive placebo, teriflunomide 7mg daily, or teriflunomide 14mg daily for 36 weeks. Eligible patients were aged 18 to 65 years, had clinically confirmed MS, had an Expanded Disability Status Scale score of 6 or less, two documented relapses in the previous 3 years, and one clinical relapse during the preceding year. The primary endpoint was the number of combined unique active lesions per MRI scan. Secondary endpoints included MRI-defined disease burden, relapse frequency, and disability increase. *Results:* Results were analyzed using the intent-to-treat

population and the safety evaluation was performed on all patients who received one or more doses of the study medication. The number of combined active lesions per scan was 0.5 with placebo, 0.2 in the teriflunomide 7mg per day group, and 0.3 in the teriflunomide 14mg per day during the study ($p < 0.01$). There was a trend toward relapse-free patients in the teriflunomide 14mg per day group compared with placebo (77% vs 62%; $p = 0.098$). The proportion of patients exhibiting disability increase was lower in the teriflunomide 14mg per day group compared with placebo (7.4% vs 21.3%; $p < 0.04$). Serious adverse events were reported in 19 patients; 7 from the placebo group, 5 from the teriflunomide 7mg group, and 7 from the teriflunomide 14mg group. These included elevated liver enzymes and hepatic dysfunction, neutropenia, rhabdomyolysis, and trigeminal neuralgia. Adverse events leading to withdrawal from the study occurred in 15 patients. Six patients were withdrawn from the study due to abnormal alanine transaminase levels (3 from placebo, 1 from teriflunomide 7mg, and 8 from teriflunomide 14mg). Alopecia, erythema multiforme, urticaria, condyloma acuminatum, dyspepsia, and hypertension led to withdrawal of one patient each for a total of 6 patients in the teriflunomide 14mg per day group.

Limitations To begin, possible conflicts of interest were not listed in this study, although Sanofi-Aventis did sponsor the study. Confidence intervals also were not reported, making it difficult to extrapolate how the rest of the population meeting the study criteria will respond to the study medication. Some of the outcomes did not reach statistical significance, possibly indicating the need for a larger study group, however, this was a Phase II study so it was understandable that the study population may be smaller.

Conclusion Teriflunomide seems to have a positive impact on the number of active MRI lesions in relapsing MS, as well as on preventing disability progression and relapse. Given this information, it is likely that teriflunomide can play an important role in therapy for patients with relapsing MS who have failed other therapies.

Contraindications^{1,2,3,4}

Pregnancy: Teriflunomide is a pregnancy category X and carries a black box warning in pregnancy. Animal studies have indicated risk of teratogenic effects or fetal death. A woman of childbearing potential must not begin treatment with teriflunomide until pregnancy is ruled out. Male-mediated toxicity may also occur. Males or females wishing to have a child should undergo an accelerated elimination procedure.

Severe hepatic disease: Patients receiving teriflunomide in severe hepatic disease may be at risk for further hepatic injury. Teriflunomide carries a black box warning for this. Patients with pre-existing acute or chronic hepatic impairment or those with serum ALT greater than 2 times the upper limit should usually not be treated with teriflunomide. Caution should be used in alcoholism, hepatitis, or jaundice.

Precautions^{1,2,3,4}

Patients with severe immunodeficiency, bone marrow dysplasia, or uncontrolled infection:

Teriflunomide may cause immunosuppression, making patients more susceptible to infections including opportunistic infections. Complete a CBC within 6 months prior to treatment initiation, and continue to monitor based on signs/symptoms of immunosuppression. If a patient develops a serious infection, consider delaying therapy and using an accelerated elimination procedure. All patients should be screened for latent TB prior to therapy.

Vaccine administration: Due to immunosuppressive effects, live vaccine administration while using teriflunomide is not recommended.

Pre-existing hypertension: Blood pressure should be checked prior to and during treatment with teriflunomide. An increase in blood pressure was reported in clinical trials.

Interstitial lung disease: Worsening of pre-existing interstitial lung disease such as bronchiolitis, eosinophilic pneumonia, hypersensitivity pneumonitis, interstitial pneumonia, pneumoconiosis, pulmonary fibrosis, or sarcoidosis of the lung. New or worsening symptoms of cough or dyspnea should be evaluated, and teriflunomide discontinued if worsening disease is confirmed.

Nursing mothers: It is not known if teriflunomide is excreted in human milk. Consider benefits of breastfeeding, risk of infant drug exposure, and risk of untreated condition. According to the manufacturer, teriflunomide should not be used in this population.

Geriatric patients: Patients over the age of 60 were not enrolled in clinical trials and may be at increased risk of peripheral neuropathy.

Diabetes mellitus: Teriflunomide may be associated with development of peripheral neuropathy. Patients with diabetes mellitus should be monitored closely for symptoms of peripheral neuropathy such as tingling in the hands or feet or bilateral numbness. If this occurs, discontinue teriflunomide and follow the accelerated elimination procedure.

Adverse Effects^{2,3,4}

Common (Occurring in at least 10% of the population)

Dermatologic

Alopecia (10%-13%)

Gastrointestinal

Diarrhea (15%-18%)

Nausea (9%-14%)

Hepatic

Elevated liver enzymes (3%-14%)

Neurologic

Headache (19%-22%)

Paresthesia (9%-10%)

Respiratory

Respiratory tract infection (9%)

Metabolic

Hypophosphatemia (5%-18%)

Other

Influenza (9%-12%)

Uncommon (Occurring in 1%-10% of the population)

Cardiovascular

Hypertension (4%)

Palpitation (2%-3%)

Neurologic

Anxiety (3%-4%)

Dermatologic

Pruritis (3%-4%)

Acne (3%)

Burning sensation (2%-3%)

Metabolic

Hyperkalemia (1%)

Gastrointestinal

Abdominal pain (5%-6%)

Toothache (4%)

Viral gastroenteritis (2%-4%)

Weight loss (2%-3%)

Abdominal distension (1%-2%)

Genitourinary

Cystitis (2%-4%)

Hematologic

Thrombocytopenia (10%)

Lymphocytopenia (7%-10%)

Leukopenia (1-2%)

Hepatic

GGT increased (3%-5%)

Neuromuscular & skeletal

Musculoskeletal pain (4%-5%)

Myalgia (3%-4%)

Sciatica (3%)

Carpal tunnel syndrome (1%-3%)

Peripheral neuropathy (1%-2%)

Ocular

Blurred vision (3%)

Conjunctivitis (3%)

Respiratory

Bronchitis (8%)

Sinusitis (6%)

Other

Herpes simplex (4%)

Seasonal allergy (2%-3%)

Cytomegalovirus hepatitis reactivation,
Jaundice, infection, MI (<1%)

Serious Adverse Events

Dermatologic

Stevens-Johnson syndrome
Toxic epidermal necrolysis

Hematologic

Neutropenia (up to 15%)

Hepatic

Liver failure

Neurologic

Peripheral Neuropathy (1.2%-1.9%)

Renal

Renal failure (1.2%)

Respiratory

Interstitial lung disease

Other

Malignancy/lymphoma

Drug Interactions^{1,4}

Warfarin

Co-administration with warfarin can cause 25% increase in peak INR.

Oral Contraceptives

May increase effects of oral contraceptives.

CYP2C8 substrates

Teriflunomide is a CYP2C8 inhibitor. Monitor for increased adverse effects from CYP2C8 substrates such as pioglitazone, rosiglitazone, paclitaxel, quinine, and naproxen

CYP1A2 substrates

Teriflunomide is a weak inducer of CYP1A2. May reduce efficacy of drugs such as tizanidine, quinine, bendamustine, tamoxifen, rasagiline, selegiline, ropinirole, propafenone, mexiletine, lidocaine, cinacalcet, anagrelide, and clozapine

Activated Charcoal

Activated charcoal binds with teriflunomide and enhances its clearance from systemic circulation via intestinal trapping. Activated charcoal is used to facilitate elimination of teriflunomide from the body when clinically necessary.

Live vaccines

Concomitant use of live vaccines is not recommended during teriflunomide use. These include herpes zoster, intranasal influenza, measles virus, mumps virus, rubella virus, varicella virus, MMR, rotavirus, typhoid, varicella virus live, and yellow fever live vaccines.

Drugs that inhibit BCRP (breast cancer resistance protein)

Teriflunomide is a substrate of ABCG2. Drugs that inhibit BCRP may cause increases in teriflunomide concentrations requiring monitoring for adverse effects and symptoms of serious liver injury and immunosuppression. These drugs include cyclosporine, eltrombopag, gefitinib, topotecan, and bosentan.

Drugs that require hepatic uptake OATP1B1 and renal uptake OAT3

Teriflunomide is an inhibitor of OATP1B1 and OAT3. Administration with drugs such as methotrexate, statins and their combination products, zidovudine, and furosemide can produce greater potential for adverse effects and hepatotoxicity.

Dosing/Administration^{1,2,3,4}

Adults: 7 or 14mg PO once daily.

Renal impairment: No dosage adjustment needed

Hepatic Impairment:

 Mild-Moderate Impairment: No dosage adjustment needed

 Severe Impairment: Use is contraindicated

Pregnancy: Use is contraindicated

Lactation: Use is not recommended. Harm to the baby cannot be ruled out.

Special Circumstances^{2,3}:

Accelerated drug elimination procedure:

1. Cholestyramine 8g orally every 8 hours for 11 days. 4g orally every 8 hours may be used if the higher dose is not tolerated.
2. 50g oral activated charcoal every 12 hours for 11 days.

Monitoring^{2,4}

- Pregnancy test prior to treatment and during treatment if pregnancy is suspected
- CBC with differential; within 6 months prior to treatment and during therapy if indicated
- Serum transaminases and bilirubin; within 6 months prior to treatment and then ALT monthly for the first 6 months of therapy
- Blood pressure prior to therapy and periodically during therapy
- Check serum potassium levels in patients with symptoms of hyperkalemia or acute renal failure

Conclusion: Teriflunomide is an effective and relatively safe therapy for patients with relapsing multiple sclerosis. It has been clinically shown to reduce relapse rates, decrease disability progression, lower the number of new or newly active brain lesions, and increase quality of life. Although it is not without adverse effects, most effects appear to be tolerable and do not lead to therapy discontinuation. Larger studies determining safety over long periods need to be completed, however current studies suggest the incidence of serious adverse events is low and long-term studies have suggested its continued safety and efficacy up to 8.5 years. Although there is no cure for multiple sclerosis, it is apparent that teriflunomide has found a place in relapsing multiple sclerosis therapy, giving patients who have tried other medications another option to help slow disease progression.

Recommended References:

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