

Teriflunomide (Aubagio)

National Drug Monograph

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VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

The mechanism of action for teriflunomide as a disease modifying therapy (DMT) in the treatment of Multiple Sclerosis (MS) is different from currently available agents.

The use of teriflunomide in monotherapy has demonstrated significantly lower annualized relapse rates (ARR), fewer lesions seen on MRI and confirmed disability progression for the 14 mg daily dose, in comparison to placebo.

The long term extension trials of the Phase II and III studies have shown the response of teriflunomide to be durable. Additionally, the safety profile during the longer exposure periods has not changed from the shorter duration trials

Early results of teriflunomide as adjunct therapy has shown that when it is added to a stable regimen of interferon-B -1a (IFNB1a) 0-80% of patients will be relapse free in comparison to IFNB1a alone. Additionally an adjunctive trial with glatiramer acetate is underway.

Commonly reported adverse events (AE) of teriflunomide include diarrhea, nausea, hair thinning and increase in ALT. None of the trials has shown a significant increase of AE in comparison to placebo or active treatment arms. Discontinuation rates were not significantly different among treatment populations.

It may take 8 months up to 2 years for teriflunomide to be cleared from the body upon discontinuation of therapy. There is an accelerated removal protocol which should be employed when faster removal is required.

Teriflunomide is an active metabolite of leflunomide. As such it bears the same warnings; pregnancy category X and a black box warning concerning hepatotoxicity.

There is an international registry of pregnancy outcomes for teriflunomide. The results of this registry have been presented in abstract form at the American Academy of Neurology meeting in 2012. There were a total of 53 pregnancies reported. Of those, no structural or functional deficits were reported.

The significant decreases in active brain lesions on MRI and reductions in ARR demonstrated with oral therapy with teriflunomide are equivalent to those outcomes seen with first line parenteral therapies (glatiramer, interferon beta).

Teriflunomide becomes the second oral agent approved by the FDA to treat relapsing forms of MS. In clinical trials it has demonstrated significantly lower annualized relapse rates (ARR), development of fewer lesions seen on MRI and confirmed disability progression for the 14 mg daily dose, in comparison to placebo. An active comparator trial with IFNB1a (Rebif) demonstrated no statistical superiority between the treatment arms for the risk of treatment failure, the primary composite endpoint of the study. Additionally, the treatment arms were not distinguishable on the endpoint of estimated annual relapse rate. There are trials currently underway which are investigating the safety and efficacy of adjunct therapy with teriflunomide in addition to IFNB1a and glatiramer. Early reports of these trials look promising.

Introduction

Teriflunomide is an oral agent approved by the FDA as a disease modifying treatment for Multiple Sclerosis (MS).

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to considering teriflunomide for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology¹⁻⁶

Teriflunomide is an active metabolite of leflunomide. It possesses both antiproliferative and anti-inflammatory properties. A key action involves teriflunomide's ability to noncompetitively and reversibly inhibit a mitochondrial enzyme (dihydro-otate dihydrogenase) which is involved in de novo pyrimidines. By blocking this enzyme, teriflunomide has a cytostatic effect on proliferating B and T cells thus suppressing activated lymphocytes. Additionally, teriflunomide inhibits protein tyrosine kinase activity which results in reducing T cell proliferation and activation with a resultant decrease in the production of cytokines.

Pharmacokinetics/Pharmacodynamics^{1,2,7}

The pharmacokinetics of teriflunomide have been investigated in multiple studies of normal volunteers. Teriflunomide is rapidly absorbed after a single dose with peak absorption occurring between 1-2 hrs post dose. The bioavailability approaches 100%. The plasma concentrations of teriflunomide were dose proportional, thus demonstrating linear pharmacokinetics. The drug is highly protein bound with a low volume of distribution. Teriflunomide demonstrates a very long elimination half life which can range from 10-18 days. The manufacturer suggests the use of a rapid elimination protocol with cholestyramine or activated charcoal when patients discontinue therapy. No difference in teriflunomide pharmacokinetics has been determined on the basis of age or gender. Additionally, in a small study of patients with multiple sclerosis, teriflunomide pharmacokinetics were not different from the normal volunteer population.

FDA Approved Indication(s) and Off-label Uses¹

Teriflunomide is indicated in the treatment of patients with relapsing forms of multiple sclerosis.

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's [Guidance on "Off-label" Prescribing](#) (available on the VA PBM Intranet site only). Clinical trials are in process investigating the potential of teriflunomide use in clinically isolated syndrome (CIS) and as adjunct therapy to other DMT used in MS treatment.

Current VA National Formulary Alternatives

Currently, the MS disease modifying agents available on the VA National Formulary are beta-interferon, glatiramer acetate, natalizumab and mitoxantrone. Additionally, fingolimod is available through the non-formulary request process.

Dosage and Administration¹

Teriflunomide is dosed at either 7mg or 14 mg given once daily.

Special Populations:

Hepatic Impairment: Teriflunomide is a metabolite of leflunomide. As such, it has the same precautions as leflunomide regarding hepatic impairment and use. Teriflunomide can be used without dose adjustment in patients with mild to moderate hepatic impairment. It is contraindicated in patients with severe hepatic impairment. Patients with preexisting liver disease may be at an increased risk of developing elevated serum transaminases when taking teriflunomide.

Renal Impairment: Teriflunomide can be used in patients with mild, moderate or severe renal failure without dosage adjustments.

Pregnancy: Teriflunomide is a pregnancy category X drug based on animal studies demonstrating fetal harm. Pregnancy must be avoided during teriflunomide treatment. If pregnancy occurs during teriflunomide treatment,

the drug should be discontinued immediately and an accelerated elimination procedure implemented in effort to reduce the fetal risk. Teriflunomide is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception.

If a patient needs to discontinue teriflunomide therapy due to serious adverse reaction (e.g., drug-induced liver injury, serious skin reactions), potential/ confirmed pregnancy or intolerance to therapy an accelerated elimination procedure with cholestyramine 8 grams every 8 hours (TID) for 11 days [if this regimen is not well tolerated, 4 grams every 8 hours (TID) can be used] or oral activated charcoal powder 50 grams every 12 hours for 11 days should be initiated. 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.

At the end of 11 days, both regimens successfully accelerated teriflunomide elimination, leading to a more than 98% decrease in teriflunomide plasma concentrations.

Efficacy

Multiple Sclerosis Efficacy Measures

Disease progression in MS is measured by several scales, with the Kurtzke Expanded Disability Status Scale (EDSS) being the most common.⁸ This scale ranges from zero to ten and progresses in increments of 0.5 degree, with higher scores indicating more severe disease. The scale allows for quantification of disability and allows neurologists to assign a functional score to affected systems, including pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other. The rate of relapse is an outcome measure in MS trials that serves as more of clinical marker of disease state. The presence of gadolinium (Gd+) enhancing lesions on MRI scans also serves as a marker of disease activity as does T2 weighted lesions. The appearance of Gd+ lesions demonstrates an “acute” inflammation, with T2 lesions being related more to disease accumulation and progression.⁹

Clinical Trials (refer to Appendix A)

Early investigations of teriflunomide include a phase II study involving 179 people over a period of 36 weeks.¹⁰ This trial investigated two different doses of teriflunomide (7 and 14 mg per day) in comparison to placebo in people with relapsing remitting MS or with secondary progressive MS with relapses. Both doses were associated with a reduction in the annualized relapse rate (ARR) however; this failed to show statistical significance. A reduction in both T-2 and gadolinium (Gd) enhancing lesions were reduced numbers of active MRI lesions and the higher dose was associated with a significantly smaller increase in disability compared to placebo. On open label extension of this trial followed patients for 144 weeks.^{11,12} Patients who had received placebo were transitioned to active drug and demonstrated a significant decrease in cumulative active lesions on MRI. The responses shown in the initial trial were durable over the duration of the extension follow up. The ARR was 0.4 per year in all groups and EDSS scores were comparable between the groups.

A randomized double blind placebo controlled Phase III trial; Teriflunomide Multiple Sclerosis Oral (TEMSO) evaluated response to teriflunomide in both relapsing patients and secondary progressive patients (N=1088).¹³ The primary outcomes of this trial were a reduction in the frequency of relapses and accumulation of disability in patients with multiple sclerosis. Patients were randomized to one of two doses for teriflunomide (7 and 14 mg) or placebo. Patients were followed for 108 weeks. Both teriflunomide doses were significantly more effective than placebo for the outcome of ARR. A significant reduction on sustained disability progression was demonstrated in the 14 mg group, as well as a significant decrease in the cumulative lesions on MRI. The most commonly reported adverse events (ADE) were diarrhea, nausea, hair thinning and elevated alanine transferase levels. These reports followed a dose response with the 14mg teriflunomide reporting higher rates of the ADE. Adverse events resulted in discontinuation rates of 8.1%, 9.8% and 10.9% for placebo, 7 mg and 14 mg of teriflunomide respectively. An open label extension of this trial is ongoing.^{14,15}

The TOWER (Teriflunomide Oral in People With Relapsing Remitting Multiple Sclerosis) study was designed to evaluate the safety and efficacy of teriflunomide (7 and 14mg doses) in comparison to placebo.¹⁶ There were 1169 patients randomized in the trial which included 189 centers across the United States and Europe. The higher dose of teriflunomide reduced relapse rates by 36% compared to placebo and reduced the risk of disability progression (sustained for 12 weeks) by 31.5%. In both treatment groups the time to first relapse was longer and more patients remained free of relapse. This was a significant result in comparison to placebo.

Teriflunomide was well tolerated with 13% of patients receiving 7mg and 15.6% of those on 14 mg discontinuing the trial due to adverse events (placebo had a 6.2% discontinuation rate).

Teriflunomide has also been compared to IFNB1a (Rebif) given subcutaneously in the TENERE (Comparing the Effectiveness and Safety of Teriflunomide and Interferon Beta-1a in Patients With Relapsing Multiple Sclerosis) trial.^{17,18} This phase III study compared two doses of teriflunomide (7 and 14 mg) with IFNB1a in 324 people over two years. The main measure of the study was the time to treatment failure, which could be the first occurrence of a relapse or withdrawal from the study. There was no statistical difference between the three groups for this measure; 48.6% on lower dose, 37.8% on higher dose of teriflunomide and 42.3% on interferon beta 1a. the rate of treatment discontinuation was higher in the interferon beta-1a group than in either of the treatment groups for teriflunomide.

Additional trials investigating the use of teriflunomide as adjunctive therapy have been undertaken. A Phase II study of teriflunomide as adjunctive therapy to glatiramer acetate in subjects with multiple sclerosis randomized 123 subjects who were already taking glatiramer acetate (Copaxone).¹⁹ Participants took one of two doses of teriflunomide or placebo for 24 weeks, in addition to their glatiramer therapy. The main aim of this study was to assess the safety of the additional treatment with teriflunomide; results showed that the drug was well tolerated. MRI studies found that adding teriflunomide did not significantly reduce the size and volume of lesions on the brain when compared to placebo. These results have not yet been published in a peer reviewed journal but only presented in abstract form.

Results from a pilot study of teriflunomide as adjunctive therapy to interferon-beta in subjects with multiple sclerosis have also been presented in abstract form.²⁰ This study randomized 116 patients to placebo or teriflunomide 7 or 14 mg in addition to their current therapy. Relapse rates were low over the duration of the study, most likely due to the fact that patients were already receiving disease modifying therapy. There was a trend to a decrease in relapse rate for both teriflunomide doses. Treatment with teriflunomide resulted in a significant decrease in T1 lesions on MRI. During subgroup analysis, the additive benefit seen with addition of teriflunomide to current therapy was most pronounced in patients who had more active disease at baseline.

Patients include in the adjunct therapy trials discussed above are being followed in a 40 week extension phase of the two studies.²¹

TOPIC is an international, multi-center, randomized, double-blind, placebo-controlled, parallel group study evaluating the efficacy and safety of 2 years' treatment with teriflunomide once daily at 7 mg and 14 mg versus placebo in approximately 780 clinically isolated syndrome (CIS) patients.²² The primary outcome of this study is the reduction of time to conversion to MS. This study is expected to be completed in 2015.

Teriflunomide is considered to be the seventh agent to enter the category of disease modifying therapies for MS. While all trials for these agents do not have the same inclusion/exclusion criteria or patient populations, it is possible to make comparisons of the agents on the basis of ARR.²³ **Table 1** compares the agents based on ARR reported in the pivotal trials for product approval.

| | Decrease in ARR |
|-----------------------------|------------------------|
| Fingolimod | 54% |
| Glatiramer | 29% |
| Interferon B 1a (IM) | 32% |
| Interferon B1a (SQ) | 32% |
| Interferon B1b | 34% |
| Natalizumab | 68% |
| Teriflunomide | 31% |

Adverse Events (Safety Data)^{1,2}**Deaths and Other Serious Adverse Events (Sentinel Events)**

Cardiovascular deaths: Four cardiovascular deaths, including 3 sudden deaths and 1 myocardial infarction in a patient with a history of hyperlipidemia and hypertension, were reported among approximately 2,600 patients exposed to teriflunomide in the premarketing database. These cardiovascular deaths occurred during uncontrolled extension studies 1 to 9 years after initiation of treatment. A relationship between teriflunomide and cardiovascular death has not been established.

Frequent adverse reactions: The most frequent adverse reactions for teriflunomide (incidence at least 10% and at least 2% greater than placebo) in the placebo-controlled studies were alopecia, ALT increased, diarrhea, influenza, nausea, and paresthesia.

Discontinuation: Alopecia was the most common cause of discontinuation because of adverse events in controlled clinical studies compared with placebo (0.5% and 1.4% of patients on teriflunomide 7 and 14 mg, respectively, and 0% on placebo).

Adverse reactions (2% or more):

| Teriflunomide Adverse Reactions ($\geq 2\%$) ¹ | | | |
|---|-------------------|--------------------|----------------------|
| Adverse reactions | Teriflunomide | | Placebo (n = 360) |
| | 7 mg (n = 368) | 14 mg (n = 358) | |
| <i>Cardiovascular</i> | | | |
| Hypertension | 4% | 4% | 2% |
| Palpitations | 3% | 2% | 1% |
| <i>CNS</i> | | | |
| Anxiety | 3% | 4% | 2% |
| Burning sensation | 2% | 3% | 1% |
| Headache | 22% | 19% | 18% |
| Paraesthesia | 9% | 10% | 8% |
| Sciatica | 1% | 3% | 1% |
| <i>Dermatologic</i> | | | |
| Acne | 1% | 3% | 1% |
| Alopecia | 10% | 13% | 3% |
| Pruritus | 4% | 3% | 2% |
| <i>GI</i> | | | |
| Abdominal distension | 2% | 1% | 0.3% |
| Abdominal pain upper | 5% | 6% | 4% |
| Diarrhea | 15% | 18% | 9% |
| Gastroenteritis viral | 2% | 4% | 1% |
| Nausea | 9% | 14% | 7% |
| Toothache | 4% | 4% | 2% |
| Weight decreased | 3% | 2% | 1% |
| <i>Hematologic/Lymphatic</i> | | | |
| Leukopenia | 2% | 1% | 0.3% |
| Neutropenia | 2% | 4% | 0.3% |
| Neutrophil count decreased | 3% | 2% | 0.3% |
| WBC decreased | 3% | 1% | 0% |

| <i>Hepatic</i> | | | |
|-------------------------------------|-----|-----|------|
| ALT increased | 12% | 14% | 7% |
| AST increased | 2% | 3% | 1% |
| Gamma-glutamyltransferase increased | 5% | 3% | 1% |
| <i>Musculoskeletal</i> | | | |
| Carpal tunnel syndrome | 1% | 3% | 0.3% |
| Musculoskeletal pain | 5% | 4% | 3% |
| Myalgia | 4% | 3% | 2% |
| <i>Respiratory</i> | | | |
| Bronchitis | 5% | 8% | 6% |
| Seasonal allergy | 2% | 3% | 1% |
| Sinusitis | 4% | 6% | 4% |
| Upper respiratory tract infection | 9% | 9% | 7% |
| <i>Special senses</i> | | | |
| Conjunctivitis | 3% | 1% | 1% |
| Vision blurred | 3% | 3% | 1% |
| <i>Miscellaneous</i> | | | |
| Cystitis | 2% | 4% | 1% |
| Influenza | 9% | 12% | 10% |
| Oral herpes | 2% | 4% | 2% |

Contraindications

No absolute contraindications have been determined for teriflunomide.

Warnings and Precautions

Hypophosphatemia: In clinical trials, 18% of teriflunomide-treated subjects had mild hypophosphatemia (at least 0.6 mmol/L and less than lower limit of normal) compared with 9% of placebo-treated subjects; 5% of teriflunomide-treated subjects had moderate hypophosphatemia (at least 0.3 and less than 0.6 mmol/L) compared with 1% of placebo-treated subjects. No subject in either treatment group had serum phosphorus less than 0.3 mmol/L.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

| NME Drug Name | Lexi-Comp | First DataBank | USP | ISMP | Clinical Judgment |
|---------------|-----------|----------------|------|------|-------------------|
| Teriflunomide | None | None | None | None | Leflunomide |
| Aubagio | None | None | None | None | none |

Drug Interactions

Teriflunomide may interact with medications metabolized by CYP2C8 or CYP1A2. The medication may interact with oral contraceptives to increase some hormone levels, with warfarin to reduce international normalized ratio,

and with tizanidine to reduce the efficacy of a given dose due to enzyme induction. Monitoring of concomitant use of medications susceptible to such interactions is necessary for patients taking teriflunomide.

Pharmacoeconomic Analysis

There are no published pharmacoeconomic trials.

Conclusions

Teriflunomide becomes the second oral agent approved by the FDA to treat relapsing forms of MS. In clinical trials it has demonstrated significantly lower annualized relapse rates (ARR), development of fewer lesions seen on MRI and confirmed disability progression for the 14 mg daily dose, in comparison to placebo. An active comparator trial with IFNB1a (Rebif) demonstrated no statistical superiority between the treatment arms for the risk of treatment failure, the primary composite endpoint of the study. Additionally, the treatment arms were not distinguishable on the endpoint of estimated annual relapse rate. There are trials currently underway which are investigating the safety and efficacy of adjunct therapy with teriflunomide in addition to IFNB1a and glatiramer. Early reports of these trials look promising.

The safety profile of teriflunomide has been demonstrated in Phase II and III trials as well as long term extensions from those studies. Since it is an active metabolite of leflunomide safety trials of that agent can be extrapolated as well. These trials have not identified any significant safety concerns. Discontinuation rates in the clinical trials have shown teriflunomide to be a well-tolerated therapy. There is a rapid removal protocol for patients who require quick removal of teriflunomide due to adverse events or pregnancy. Although teriflunomide carries a pregnancy category X rating, a pregnancy registry has not demonstrated an increase in neonatal deficits as a result of teriflunomide exposure.²

On the basis of currently available data, teriflunomide displays a favorable risk/benefit ratio. There is data to demonstrate that the efficacy of teriflunomide monotherapy produces results similar to currently available agents. Trials evaluating teriflunomide adjunct therapy and use in CIS are underway and early reports are promising.

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Appendix A: Clinical Trials of teriflunomide

| Citation | Study design | Duration | Treatment | MS type | Efficacy Results | Safety Results |
|--------------------|--|-----------|---|---------|---|---|
| Phase II | MC, DB, PC N=179 | 36 weeks | T 7mg, T14 mg, placebo | RMS | Median number of active MRI lesions 7mg 0.2 (p<0.03) 14 mg 0.3 (p<0.01) Placebo 0.5 | No reported deaths AE were reported in all treatment groups with incidence and severity comparable across groups |
| Phase II extension | Long term extension of trial above, N=147 | | T 7mg, T14 mg Patients on placebo were randomized to a treatment group | RMS | ARR decreased over 372 week evaluation period Minimal disability progression | Well tolerated with up to 8.5 yrs of exposure One death reported |
| TEMSO | MC, DB, PC N=1088 | 108 weeks | T 7mg, T14 mg, placebo | RMS | Both doses of T reduced adjusted ARR by 31% vs. placebo (p<0.001) Sustained disability reduced by 30% in T 14mg group (p=0.03) Reduction in lesion volume T 7mg 39.4% (p=0.03) T 14mg 67.4% (p<0.001) | Most common AE in treatment groups; diarrhea, nausea, hair thinning, ALT increases No deaths reported in 2yr trial Discontinuation rates T7 mg T14 mg |
| TEMSO extension | N=742 | | T 7mg, T14 mg Patients on placebo were randomized to a treatment group | RMS | ARR remained low Placebo/T7 mg 0.251 T 7mg 0.234 Placeb/14 mg 0.182 T 14 mg 0.206 Changes in total MRI lesion volume trended lower in the continuous therapy groups | Incidence of AE were similar across treatment groups Generally well tolerated 2 deaths reported |
| TENERE | MC, DB, parallel group N=324 | 48 weeks | T 7mg T 14mg Rebif 44 ug three times weekly | RMS | <u>Rate of failure</u> T 7mg 48.6% T 14mg 37.8% Rebif 42.3% <u>ARR</u> | Permanent discontinuations T 7mg 6.4% T 14mg 13.5% Rebif 24% |

| Citation | Study design | Duration | Treatment | MS type | Efficacy Results | Safety Results |
|------------------------|----------------------|------------|---|---------|---|--|
| TOWER | MC, DB, PC N=1169 | ≥ 48 weeks | T 7mg, T 14mg, placebo | RMS | T 7mg 0.41 T 14mg 0.26 Rebif 0.22 Reduction in ARR T 7mg 22.3%, p=0.0189 T 14 mg 36.3% p=0.001 Sustained 12 week disability progression T 14mg 31.5% p=0.0442 | Most common AE in treatment groups; diarrhea, nausea, hair thinning, ALT increases |
| Adjunctive to Rebif | MC, DB, PC N=118 | ≥ 48 weeks | Rebif added to either T 7mg, T 14mg, placebo | RMS | Trend toward lower relapse rates in T 7mg and 14mg T1 lesions (number) T 7mg RRR 84.6% p=0.0005 T 14mg RRR 82.8% p<0.001 | Discontinuation rates Placebo 4.9% T 7mg 8.1% T 14mg 7.9% Reported AE similar to those in previous trials |