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Formulary Drug Reviews

Teriflunomide

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Generic Name:	TERIFLUNOMIDE
Proprietary Name:	*Aubagio* (sanofi-aventis)
Approval Rating:	1S
Therapeutic Class:	Immunomodulators, Dihydroorotate Dehydrogenase Inhibitors
Similar Drugs:	Leflunomide
Sound- or Look-Alike Names:	Leflunomide

INDICATIONS

Teriflunomide is approved for the treatment of relapsing forms of multiple sclerosis (MS).[1] Current therapies for relapsing MS include fingolimod, glatiramer acetate, interferon beta-1a, interferon beta-1b, mitoxantrone, and natalizumab.[2-4] **Table 1** lists the US Food and Drug Administration (FDA)-approved therapies for relapsing MS by mechanism of action and pharmacologic class. Additionally, rituximab is used off-label for the treatment of relapsing remitting MS.[3]

MS is one of the most common acquired inflammatory demyelinating neurological diseases of the central nervous system (CNS) in young adults. It is a chronic, progressive, degenerative neurological disease that presents with demyelination and axonal damage within the CNS. It is more prevalent in women and White patients of northern European descent.[5,6] The disease can manifest a variety of neurologic symptoms, including cognitive impairment, incontinence, visual disturbances, and impaired movement.

The exact cause of MS is unknown, but it is thought to be caused by the response from the cellular and humoral arms of the immune system combined with environmental triggers and genetic susceptibility. When the peripherally activated myelin-specific T cells gain access to the CNS, they are able to disrupt the myelin because of the changes created in the blood-brain barrier by various inflammatory mediators and other factors. This process results in the release of antigens specific to the CNS, development of myelin

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Table 1. FDA-approved therapies for relapsing multiple sclerosis with corresponding mechanism of action and pharmacologic category[1,2,5,7,8]

	Mechanism of action	Pharmacologic category
Fingolimod	Prevents the release of lymphocytes from lymph nodes, reducing the number of lymphocytes and inflammation within the CNS	Sphingosine 1-phosphate receptor modulator
Glatiramer acetate	Induces and activates T-lymphocyte suppressor cells specific to myelin antigen and interferes with antigen-presenting function of immune cells opposing pathogenic T-cell function	Biologic
Interferon beta-1a	Alters the expression and response of surface antigens and enhances immune cell activities	Interferon
Interferon beta-1b	Alters the expression and response of surface antigens and enhances immune cell activities	Interferon
Mitoxantrone	Inhibits B-cell, T-cell, and macrophage proliferation; impairs antigen presentation secretion of interferon gamma, tumor necrosis factor-alpha, and IL-2	Antineoplastic agent, anthracenedione
Natalizumab	Blocks T-lymphocyte migration into CNS	Monoclonal antibody, selective adhesion-molecule inhibitor (alpha-4-adhesion)
Teriflunomide	Inhibits B- and T-cell proliferation, activation, and production of cytokines	Dihydroorotate dehydrogenase inhibitor

Note: CNS = central nervous system; FDA = US Food and Drug Administration; IL-2 = interleukin 2.

antibody-forming B cells, and a cascade of inflammatory mediators that drive disease progression in MS patients.[5]

Among the 4 clinical subtypes of MS (relapsing remitting, primary progressive, secondary progressive, and progressive relapsing), the majority (approximately 85%) of patients have the relapsing remitting form. As disease progression occurs, neurological function continues to decrease and the patient converts to progressive MS.[5,6]

CLINICAL PHARMACOLOGY

Teriflunomide is a novel, orally bioavailable, active metabolite of leflunomide that has antiproliferative and anti-inflammatory activity.[1,5,7-9] Through noncompetitive, selective, and reversible inhibition, teriflunomide inhibits the mitochondrial enzymatic activity of dihydroorotate dehydrogenase. Dihydroorotate dehydrogenase functions as the rate-limiting enzyme in de novo pyrimidine synthesis. Inhibition of pyrimidine synthesis selectively produces a cytostatic effect on proliferating T and B lymphocytes in the periphery, while avoiding undue cytotoxicity to other cell types.[5,7]

Teriflunomide effectively reduces B-lymphocyte proliferation by direct suppression of dihydroorotate dehydrogenase and reduction of lipopolysaccharide-induced proliferation via the secretion of immunoglobulin M (IgM) from B cells. Additionally, independent of teriflunomide activity, B-cell proliferation is suppressed by an interleukin 4 class switch into IgG1. In other words, teriflunomide changes T and B cell communication, causing B cells to secrete IgG antibodies rather than IgM antibodies. This is an antibody class type switch. The interaction between B and T lymphocytes is effectively inhibited by teriflunomide; thus, blockade of T lymphocyte–dependent antibody production occurs. Teriflunomide has also been implicated in the function modification of CD43 and leukocyte function–associated antigen 1 on T lymphocytes and the interference of T-lymphocyte activation upon presentation of antigen presenting cells. The end result is impaired activation of T cells because of blocking of calcium signals from intercellular signaling.[5,7] The risk of clinically significant cytopenia or depletion of nucleic acid essential cellular functions is minimal because of the synthesis of pyrimidine nucleotides through a salvage pathway that is independent of dihydroorotate dehydrogenase enzymatic activity.[5,7] Additionally, pyrimidine nucleotides have an essential function in phospholipid biosynthesis, glycosylation of proteins, and DNA repair. This suggests that the inhibition of pyrimidine synthesis and the subsequent decrease in cellular pools of pyrimidine may decrease the synthesis of cellular mediators that are essential to an aberrant immune response, which is essential to the pathophysiology of MS.[5,7]

The inhibition of de novo pyrimidine synthesis by teriflunomide can be countered by an increased concentration of the prototypic pyrimidine nucleoside uridine. In vitro studies have shown a reversal of teriflunomide effects when exogenous uridine is added to proliferating immune cells.[7,10] However, the production of cytokines, antigen expression, and inappropriate cellular migration are still impaired despite the restoration of proliferative response.[7,10,11] In a murine model, it decreased T-cell proliferation because of the inhibition effect of Janus-associated kinases Jak1 and Jak3; these Janus tyrosine kinases function as the primary cytokine receptors in the IL-2–dependent T-cell lineage.[7] Additional targets of teriflunomide include the inhibition of the Src family of tyrosine kinases; epidermal growth factor-receptor tyrosine kinases; multiple members of the mitogen-activated protein kinase pathway, including p38 and Jak; maintenance of B-cell leukemia 2 and B-cell lymphoma extra large; inducible nitric oxide synthase expression; nuclear factor-kappaB; and cyclooxygenase 2 (COX-2).[7,12-15] The inhibitory function of teriflunomide in the previously listed kinase activity and COX-2 activity has been demonstrated in vitro primarily with higher concentrations that also produce dihydroorotate dehydrogenase inhibition.[7,10-15]

PHARMACOKINETICS

The oral bioavailability of a single dose of teriflunomide in healthy, fasted patients is 100%, and the median time to reach peak plasma concentrations occurs within 1 to 4 hours.[1,16] Coadministration with food does not result in a clinically significant effect on pharmacokinetic parameters; however, absorption may be delayed by approximately 6 hours.[1,16]

The volume of distribution of teriflunomide is 11 L.[1,16] Teriflunomide is primarily distributed in the periphery and has limited blood-brain barrier penetration.[5] Protein binding is approximately 99%, predominantly to albumin.[1] The median half-life of teriflunomide is approximately 18 and 19 days following consecutive doses of 7 and 14 mg, respectively, and steady-state concentrations are reached in approximately 12 weeks.[1]

Teriflunomide is the major moiety detected in the plasma. The metabolic biotransformation of teriflunomide primarily involves hydrolysis with multiple secondary metabolic pathways, including oxidation, N-acetylation, and sulfate conjugation.[1,5,16] Three weeks after administration of a single oral dose of ^{14}C-radiolabeled teriflunomide in healthy volunteers, 37.5% was excreted as unchanged drug in the feces and 22.6% (predominately as the 4-trifluoro-methyl-aniline oxanilic acid metabolite) was excreted in the urine.[1,16] Extensive enterohepatic recirculation results in a total plasma clearance of approximately 0.5 L/h.[17] Administration of activated charcoal or cholestyramine accelerates elimination, decreasing the half-life to 1 to 2 days. An accelerated elimination procedure with cholestyramine resulted in an additional 23.1% teriflunomide recovery, primarily in the feces.[1,16]

COMPARATIVE EFFICACY

Indication: Treatment of Multiple Sclerosis With Teriflunomide Monotherapy

Studies

Drug: Teriflunomide vs Placebo
Reference: O'Connor PW, et al, 2006[18]
Study Design: Randomized, double-blind, placebo-controlled, parallel-group, multicenter study in Canada and France
Study Funding: sanofi-aventis
Patients: 179 adult patients with clinically confirmed relapsing remitting or secondary progressive MS, an Expanded Disability Status Scale (EDDS) score of 6 or less, 2 documented relapses in the previous 3 years, and 1 clinical relapse during the preceding year.
Intervention: All patients had a 4-week treatment-free screening period prior to randomization. Randomization was done 1:1:1 to teriflunomide 7 mg, teriflunomide 14 mg, or placebo daily. All patients received a loading dose of twice their scheduled maintenance dose of the assigned medication during the initial 7 days of treatment followed by the assigned dose for the remaining 35 weeks. Compliance was 99.2% in the teriflunomide 7 mg/day group, 98.8% in the teriflunomide 14 mg/day group, and 99.2% in the placebo group.
Results:
Primary Endpoint(s):

- Median number of combined unique active lesions, including new or enlarging T2 lesions and gadolinium-enhancing T1 lesions, per magnetic resonance imaging (MRI) scale, was 0.5 in the placebo treatment group, 0.2 in the teriflunomide 7 mg treatment group ($P < .03$), and 0.4 in the teriflunomide 14 mg treatment group ($P < .01$) at 35 weeks.

Secondary Endpoint(s):

- Patients treated with teriflunomide had fewer T1-enhancing lesions, new or enlarging T2 lesions, and new T2 lesions per scan than placebo in both treatment groups.

- At 35 weeks, only patients in the teriflunomide 14 mg treatment group had reduced T2 lesion volume (an indicator of burden of disease) compared with placebo ($P = .0106$).
- The teriflunomide 14 mg treatment group also had a trend toward fewer relapses (77% vs 62%; $P < .098$), less use of corticosteroids to treat a relapse (14% vs 23%; not significant), and less of an increase in their EDDS score (7.4% vs 21.3%; $P < .04$).

Comments: A total of 147 patients who completed the initial study were enrolled in the extension study to further evaluate the long-term safety of teriflunomide. Patients originally randomized to placebo were subsequently reallocated to teriflunomide 7 or 14 mg, according to the predefined randomization schedule. Patients who were originally randomized to teriflunomide continued their assigned treatment. The mean duration of study treatment, including both the core and extension phase, from baseline to the interim cutoff was 5.6 years. Annual relapse rate, disability progression, and MRI activity remained low throughout the entire course of the extension trial. A trend of dose-dependent benefits with teriflunomide 14 mg on several MRI parameters was observed.[19] Reduction in disease activity with teriflunomide was maintained for up to 8 years, and the relapse rate and disability progression remained low in these patients.[20]

Reference: O'Connor P, et al, 2011 (TEMSO trial)[8]
Study Design: Randomized, double-blind, placebo-controlled, parallel-group, multicenter, international study
Study Funding: sanofi-aventis
Patients: 1,088 adult patients with MS with a confirmed relapsing clinic course, with or without progression, an EDDS score of 5.5 or less, 2 documented relapses in the previous 2 years, and 1 clinical relapse during the preceding year.
Intervention: Teriflunomide 7 or 14 mg or placebo daily for 108 weeks. Patients were permitted to be treated to IV glucocorticoids per neurologist discretion for suspected or confirmed relapses.
Results:
Primary Endpoint(s):

- The annual rate of relapse was 0.54, 0.37, and 0.37 for placebo, teriflunomide 7 mg, and teriflunomide 14 mg, respectively ($P < .001$, for both comparisons with placebo), in the intent-to-cohort.

Secondary Endpoint(s):

- The annual rates of relapse correspond to a relative reduction of 31.2% ($P < .001$) for teriflunomide 7 mg and 31.5% ($P < .001$) for teriflunomide 14 mg.
- Sustained disease progression for at least 12 weeks was 27.3% in the placebo treatment arm, 21.7% in the teriflunomide 7 mg treatment arm ($P = .08$), and 20.2% in the teriflunomide 14 mg treatment arm ($P = .03$).
- The hazard ratio (HR) reduction for sustained progression was only reduced in the teriflunomide 14 mg treatment arm compared with placebo (29.8% relative reduction; $P = .03$).
- The change in total lesion volume from baseline was lower in the teriflunomide treatment arms compared with placebo (39.4% with teriflunomide 7 mg vs placebo [$P = .03$] and 67.4% with teriflunomide 14 mg vs placebo [$P < .001$]).
- Both active-treatment groups had fewer gadolinium-enhancing lesions per T1-weighted scans and unique active lesions per scan were observed in contrast with placebo ($P < .001$).

Comments: The dropout rate was high in all 3 treatment groups: 28.7% for placebo, 25.1% for teriflunomide 7 mg, and 26.6% for teriflunomide 14 mg.[8] Other results have been presented only as meeting abstracts, including analysis of these data from this study regarding health care resource utilization and safety data from the extension phase of the study. The analysis of health care resource utilization found hospitalizations were reduced by 36% with teriflunomide 7 mg ($P = .015$ vs placebo) and 59% with teriflunomide 14 mg ($P < .001$ vs placebo); risk of hospitalization per relapse was reduced by 6% with teriflunomide 7 mg (not significant vs placebo) and 43% with teriflunomide 14 mg ($P < .001$ vs placebo); and the annualized rate of relapses requiring corticosteroids was decreased by 29% with teriflunomide 7 mg ($P = .0014$ vs placebo) and 34% with teriflunomide 14 mg ($P < .001$ vs placebo).[21,22] The extension phase found both teriflunomide doses to be well tolerated and the pattern of adverse reactions to be consistent with the core 2-year Teriflunomide Multiple Sclerosis Oral (TEMSO) study in patients treated for up to 4 years with teriflunomide therapy; the beneficial effects on clinical and MRI endpoints were maintained for up to 5 years.[23,24]

Reference: TOWER trial[9,25,26]
Study Design: Randomized, double-blind, placebo-controlled, parallel-group, international, multicenter study

Study Funding: sanofi-aventis
Patients: 1,169 adult patients with relapsing MS with 2 documented relapses in the previous 2 years.
Intervention: Teriflunomide 7 or 14 mg or placebo daily for a minimum of 48 weeks. The average exposure to teriflunomide was 18 months.
Results:
Primary Endpoint(s):
- 36.3% reduction in annualized relapse rate was observed in the teriflunomide treatment groups compared with placebo ($P < .001$).

Secondary Endpoint(s):
- 22.3% reduction in annualized relapse rate was observed in the 7 mg treatment group versus placebo ($P = .02$).
- 31.5% reduction in the risk of 12-week sustained accumulation of disability, as measured by the EDDS score, was observed in the teriflunomide treatment groups compared with placebo ($P = .0442$).

Comments: Study is complete; however, results have not been published.

Drug: Teriflunomide vs Placebo With Interferon Beta-1a (*Rebif*)
Reference: TENERE trial[27,28]
Study Design: Randomized, open-label, rater-blind, active comparative, parallel-group, multicenter study
Study Funding: sanofi-aventis
Patients: 324 adult patients with a clinical diagnosis of a relapsing form of MS and an EDDS score of 5.5 or less.
Intervention: Teriflunomide 7 or 14 mg or interferon beta-1a (up to 44 mcg, subcutaneous injection 3 times per week) until time to failure, defined as the first occurrence of relapse or permanent study treatment discontinuation for any cause, whichever came first. Duration of treatment was capped at 115 weeks, with a prespecified trial stoppage when the last patient enrolled had been treated for 48 weeks.
Results:
Primary Endpoint(s):
- Treatment failure was documented in 37.8% of patients in the 14 mg treatment group, 48.6% in the 7 mg treatment group, and 42.3% in the interferon monotherapy treatment group (HR, 0.56; 95% confidence interval [CI], 0.56 to 1.31). Time to failure was the primary endpoint; average was 20 months.

Secondary Endpoint(s):
- Relapses were observed in 15.4% of patients in the interferon monotherapy treatment group, 42.2% in the 7 mg treatment group, and 23.4% in the 14 mg treatment group.
- Annualized relapse rates were 0.26 for the 14 mg treatment group (not significant), 0.41 for the 7 mg treatment group ($P = .03$ vs placebo), and 0.22 for the interferon monotherapy treatment group.
- Mean fatigue scores were lower in the 7 mg treatment group compared with the interferon treatment group (0.97 vs 9.1; $P = .03$).
- Global patient-reported satisfaction with treatment was higher in both teriflunomide treatment groups.

Comments: Study results have only been published as an abstract. The overall safety and efficacy profile observed in the Study Comparing the Effectiveness and Safety of Teriflunomide and Interferon Beta-1a in Patients With Relapsing Multiple Sclerosis (TENERE) was similar to other published studies; however, the primary outcome of reducing treatment failures over a continuous time frame failed to be achieved compared with interferon. Patients were allowed to enroll in an extension treatment phase after the study; these were patients who completed the initial treatment period. It provided them an opportunity to continue or switch to teriflunomide 14 mg for 48 weeks or until teriflunomide became commercially available.

Indication: Treatment of Multiple Sclerosis With Adjunctive Teriflunomide Therapy

Studies

Drug: Teriflunomide vs Placebo Added to Interferon Beta
Reference: Freedman MS, et al, 2012[29,30]
Study Design: Randomized, double-blind, placebo-controlled, parallel-group, international, multicenter study
Study Funding: sanofi-aventis
Patients: 116 adult patients with relapsing remitting, secondary progressive, or progressive relapsing MS; an EDDS score of 5.5 or less; no relapse for 8 weeks; and clinically stable condition for 4 weeks before study.
Intervention: Teriflunomide 7 or 14 mg or placebo daily for 24 weeks. All patients were maintained on stable interferon beta-1a or interferon beta-1b therapy. Following completion of the initial 24 weeks, patients could elect to enter an additional 24-week blinded extension trial, during which patients continued to receive their originally assigned treatment.

Results:
Primary Endpoint(s):
- Safety and tolerability of teriflunomide plus interferon beta was the primary endpoint.
- The tolerability of teriflunomide with interferon beta therapy was acceptable; the most common treatment-emergent adverse events included increased alanine aminotransferase (ALT), diarrhea, urinary tract infection, fatigue, nasopharyngitis, headache, decreased lymphocyte count, and decreased white blood cell (WBC) count.
- The incidence of adverse events was slightly higher with the teriflunomide 7 mg plus interferon beta group compared with the teriflunomide 14 mg and placebo groups.
- After 48 weeks, there appeared to be a dose-related effect on ALT (increased levels), blood pressure (increased), and lymphocyte count (decreased).
- Infections and hematologic disorders were higher in the teriflunomide groups (56.9% with 7 mg and 52.6% with 14 mg) compared with the placebo group (39%). However, none of these led to discontinuation of drug therapy.
- The discontinuation rate was similar at 24 weeks (2.4% with placebo plus interferon beta, 2.7% with teriflunomide 7 mg plus interferon beta, and 2.6% with teriflunomide 14 mg plus interferon beta). The incidence of discontinuation increased during the 24-week extension phase of the trial: 4.9%, 8.1%, and 7.9%, respectively.

Secondary Endpoint(s):
- Annualized relapse rate: 0.408 per patient-year in the placebo treatment group, 0.285 in the teriflunomide 7 mg treatment group, and 0.169 in the teriflunomide 14 mg treatment group. The adjusted annualized relapse rates were 0.343, 0.231, and 0.144, respectively.
- 32.6% relative decrease in the adjusted annualized relapse rate in the 7 mg treatment group ($P = .4355$) and 57.9% in the 14 mg treatment group ($P = .101$) at 48 weeks compared with placebo.
- A greater reduction in the number of T1-gadolinium–enhancing lesions per scan at week 48 was observed in both teriflunomide treatment groups compared with placebo. Relative risk (RR) reduction of 84.6% with teriflunomide 7 mg ($P < .001$) and 82.8% with teriflunomide 14 mg ($P < .001$) was observed compared with placebo.
- The total of T1-gadolinium–enhancing lesions was reduced in the 14 mg treatment group at week 24 (RR reduction, 64.7%; $P = .007$) and at week 48 (RR reduction, 70.6%; $P = .015$).
- Patients in teriflunomide treatment groups demonstrated an increased number of scans that were free of gadolinium-enhancing lesions and reported fewer relapses during the treatment period compared with interferon beta monotherapy.

Comments: An ongoing trial, Efficacy and Safety of Teriflunomide in Patients With Relapsing Multiple Sclerosis and Treated With Interferon-Beta (TERACLES), is currently recruiting approximately 1,455 patients to further investigate concomitant therapy with teriflunomide and interferon beta to provide superior disease control. An anticipated study completion date is April 2014.[31]

Drug: Teriflunomide vs Placebo With Glatiramer Acetate
Reference: Freedman M, et al, 2010[32]
Study Design: Randomized, placebo-controlled study
Study Funding: sanofi-aventis
Patients: 123 adult patients with relapsing remitting MS.
Intervention: Teriflunomide 7 or 14 mg or placebo daily for 24 weeks. All patients were maintained on stable during ongoing glatiramer acetate therapy.
Results:
Other Endpoint(s):
- The number of gadolinium-enhancing lesions per T1-weighted scan was higher in the 7 mg treatment arm (28.6%) compared with the placebo (14.6%) and 14 mg (12.8%) treatment arms at baseline.
- After 24 weeks of treatment, the addition of teriflunomide to the glatiramer acetate therapy decreased the number of lesions in the 7 mg treatment arm ($P = .011$) and decreased the lesion volume in the 14 mg treatment arm ($P = .039$) compared with glatiramer acetate monotherapy; details on the changes from baseline or placebo were not provided in the report.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

Teriflunomide therapy is contraindicated in patients with severe hepatic impairment because of the risk of severe liver injury, including fatal liver failure and dysfunction. The product labeling includes a boxed warning regarding the increased risk of severe liver injury in patients with preexisting liver disease and in patients taking concomitant hepatotoxic drugs. If

teriflunomide liver injury is suspected, an accelerated elimination procedure with cholestyramine or activated charcoal may be initiated.[1]

Based on animal data, teriflunomide has been shown to be selectively teratogenic and embryolethal (Pregnancy Category X). Teriflunomide therapy is contraindicated in pregnant women or in women of childbearing potential utilizing an unreliable method(s) of contraception. A boxed warning is included in the product labeling regarding the risk of teratogenicity. If pregnancy occurs during treatment, teriflunomide should be discontinued and an accelerated elimination procedure should be immediately initiated. It is recommended that all women of childbearing potential undergo an accelerated elimination procedure following teriflunomide therapy to achieve plasma concentrations less than 0.02 mg/L. Health care providers are encouraged to enroll pregnant women exposed to teriflunomide into the *Aubagio* pregnancy registry to monitor fetal outcomes. Teriflunomide is detected in human semen; a reliable method of contraception is recommended to minimize the risk of pregnancy. Discontinuation of therapy and initiation of an accelerated elimination procedure to decrease plasma concentrations to less than 0.02 mg/L is recommended for male patients who wish to father a child.[1]

Concomitant therapy with leflunomide is contraindicated.[1]

Warnings and Precautions

Severe liver injury, including fatal liver failure and dysfunction, has been reported with leflunomide therapy and may occur with teriflunomide because it is the active metabolite of leflunomide. Patients with preexisting liver disease may be at increased risk of hepatic injury. The drug should be avoided in patients with preexisting acute or chronic liver disease or those with serum ALT greater than 2 times the upper limit of normal (ULN).[1]

Plasma elimination of teriflunomide under normal conditions is approximately 8 months; however, based on individual variation, it may take up to 2 years. An 11-day treatment course of cholestyramine or activated charcoal outlined in the product labeling results in a greater than 98% decrease of initial teriflunomide plasma concentrations.[1]

A mean decrease in WBC count and in platelet count has been observed with administration of teriflunomide 7 and 14 mg. Decreases in WBC count were observed during the first 6 weeks of therapy and remained low throughout treatment. Teriflunomide therapy is not recommended in patients with severe immunodeficiency, bone marrow disease, or severe, uncontrolled infections because of the increased risk of opportunistic infections. Teriflunomide therapy should be delayed in patients with active acute or chronic infections until the infection is resolved.[1]

Immunosuppressive medications have been associated with increased risk of malignancy, particularly in lymphoproliferative disorders. Teriflunomide trials reported no apparent increased incidence of malignancies or lymphoproliferative disorders; however, a theoretical risk exists.[1]

Vaccination with live vaccines is not recommended with ongoing teriflunomide therapy. Additionally, administration of live vaccines following teriflunomide therapy should be carefully considered because of the drug's slow elimination and immunosuppressive properties.[1]

Peripheral neuropathy, including both polyneuropathy and mononeuropathy, has been reported with teriflunomide therapy. Increased risk of peripheral neuropathy may be observed in patients taking neurotoxic medication, elderly patients (60 years and older), and patients with diabetes. Discontinuation of therapy and initiation of an accelerated elimination procedure should be considered if a patient develops symptoms consistent with peripheral neuropathy, including bilateral numbness or tingling of hands or feet.[1]

Transient acute renal failure, potentially due to acute uric acid nephropathy, with a serum creatinine measurement increase of 100% or greater from baseline values has been observed with teriflunomide therapy.[1]

Treatment-emergent hyperkalemia, defined as plasma potassium greater than 7 mmol/L, was reported in 8 of 829 teriflunomide-treated patients, 2 of whom were diagnosed with acute renal failure.[1]

Stevens-Johnson syndrome, toxic epidermal necrolysis, and development or worsening of preexisting interstitial lung disease have been reported with patients who were administered leflunomide. A theoretical risk is expected with teriflunomide. Discontinuation of therapy with an accelerated elimination procedure should be considered in a patient who develops symptoms consistent with each respective diagnosis.[1]

An increase in baseline blood pressure was reported in clinical trials. Appropriate management of elevated blood pressure is recommended during teriflunomide therapy.[1]

Patients administered another agent with known potential hematologic suppression (eg, antineoplastic or immunosuppressive therapies) should be carefully monitored for hematologic toxicity.[1]

Table 2. Most frequent adverse reactions from study 1 (108-week, placebo-controlled, clinical study of 1,086 patients with relapsing multiple sclerosis)[1]

Adverse reactions	Teriflunomide 14 mg (n = 358)	Teriflunomide 7 mg (n = 368)	Placebo (n = 360)
Headache	19%	22%	18%
Diarrhea	18%	15%	9%
Nausea	14%	9%	7%
ALT increased	14%	12%	7%
Alopecia	13%	10%	3%
Influenza	12%	9%	10%
Paresthesia	10%	9%	8%
Upper respiratory tract infection	9%	9%	7%
Bronchitis	8%	5%	6%
Sinusitis	6%	4%	4%
Abdominal pain, upper	6%	5%	4%

Note: ALT = alanine aminotransferase.

Breast-feeding is not recommended while taking teriflunomide. The drug was detected in rat milk following a single dose of teriflunomide. Therefore, the manufacturer recommends discontinuing either breast-feeding or the drug to avoid any serious adverse reactions to the breast-feeding infant.[1]

The safety and effectiveness of teriflunomide in pediatric patients have not been established.[1]

ADVERSE REACTIONS

Common adverse reactions observed in placebo-controlled trials (occurring with a frequency of 10% or greater and a rate of 2% or greater than reported with placebo therapy) include elevated ALT, alopecia, diarrhea, influenza, nausea, and paresthesia. Alopecia was the most common cause of discontinuation of teriflunomide treatment compared with placebo. **Table 2** summarizes the adverse reactions that occurred in 5% or more of the teriflunomide-treated patients.[1]

DRUG INTERACTIONS

Coadministration of teriflunomide and warfarin results in a 25% decrease in the peak international normalized ratio (INR). It is recommended to closely monitor and appropriately adjust the dose of warfarin based on INR results.[1]

Ethinyl estradiol and levonorgestrel peak concentrations and mean exposure are increased following repeated doses of teriflunomide. Careful consideration of oral contraceptive therapy, including specific type and dosage, is recommended with concomitant teriflunomide therapy.[1]

Teriflunomide is an inhibitor of cytochrome P450 (CYP-450) 2C8. It is recommended that patients undergoing concomitant therapy with a drug metabolized by CYP2C8, such as repaglinide, paclitaxel, pioglitazone, and rosiglitazone, be monitored for toxicity because of increased substrate drug exposure.[1]

Teriflunomide is a weak inducer of CYP1A2. Therefore, drug interactions involving substrates metabolized by this pathway may occur. Patients should be monitored when teriflunomide is coadministered with drugs such as duloxetine, alosetron, theophylline, and tizanidine, because therapeutic efficacy may be reduced.[1]

Resistant protein (breast cancer–resistance protein [BCRP]) inhibitors (eg, cyclosporine, eltrombopag, gefitinib) may increase exposure to teriflunomide. In addition, teriflunomide is an inhibitor of BCRP.[1]

RECOMMENDED MONITORING

It is recommended that within 6 months prior to the initiation of teriflunomide therapy, serum transaminase and bilirubin levels be obtained. ALT levels should be monitored at least monthly once therapy is initiated for the first 6 months of therapy. Concomitant therapy with other potentially hepatotoxic drugs may warrant additional monitoring. If serum transaminase increases to greater than 3 times the ULN, the patient develops symptoms suggestive of hepatic dysfunction, or liver injury is suspected, consider discontinuing teriflunomide therapy and initiating an accelerated elimination procedure. In these patients, liver function tests should be monitored weekly until they are normalized.[1]

Because of the potential risk of teratogenicity and embryolethal effects with teriflunomide therapy, women of childbearing potential must not initiate therapy until pregnancy is excluded and a reliable method of contraception is verified.[1]

A complete blood cell count panel should be obtained within 6 months of initiating teriflunomide therapy, and it is recommended that patients be monitored for signs and symptoms indicative of bone marrow suppression. Additionally, a tuberculin skin test should be conducted prior to initiating therapy to effectively rule out latent tuberculosis. Patients who test positive should be treated according to standard medical practice prior to initiation of teriflunomide therapy.[1]

Serum potassium levels, renal function, and blood pressure should be monitored throughout therapy and appropriately managed.[1]

Additional monitoring parameters may include clinical markers and symptoms of disease progression.

DOSING

The approved dosage of teriflunomide is 7 or 14 mg orally once daily with or without food.[1]

No dosage adjustments are necessary in patients with mild to moderate hepatic impairment or in patients with mild to severe renal impairment.[1] Females have a 23% decrease in clearance, but no dosage adjustments have been recommended.[1]

PRODUCT AVAILABILITY

A new drug application was accepted for review by the FDA in October 2011.[6] Teriflunomide was approved by the FDA on September 12, 2012.[33]

Teriflunomide is available as 7 and 14 mg film-coated tablets in cartons of 5 and 28 tablets in blister cards.[1] Each tablet also includes lactose monohydrate, corn starch, hydroxypropylcellulose, microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The film coating of the tablets contains hypromellose, titanium dioxide, talc, and polyethylene glycol. In addition, the film coating of the 7 mg tablet contains iron oxide yellow and the 14 mg tablet contains indigo carmine aluminum lake.[1]

Tablets should be stored at controlled room temperature (20°C to 25°C [68°F to 77°F]); excursions are permitted between 15°C and 30°C (59°F and 86°F).[1]

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for teriflunomide.[33]

The manufacturer is required to complete a post-marketing study to determine the safety and efficacy of teriflunomide in pediatric patients and a prospective, observational exposure cohort study in the United States that compares the maternal, fetal, and infant outcomes of women with MS exposed to teriflunomide during pregnancy with unexposed control populations. In addition, the FDA is requiring a summary analysis of the pooled safety results from the Efficacy Study of Teriflunomide in Patients With Relapsing Multiple Sclerosis (TOWER) and Study 6049 clinical trials, with a specific focus on the effect of teriflunomide on bicarbonate, magnesium, and calcium levels and acute renal failure and a drug interaction study with rosuvastatin.[33]

CONCLUSION

Teriflunomide represents a novel therapeutic approach to the regulation of B- and T-lymphocyte response in patients with MS. Based on the pathophysiology of MS, current treatments attempt to reduce the cellular immune response to myelin within the CNS. However, no current therapy has proved to be curative, and disease progression is often unavoidable. Teriflunomide has the advantage of being an oral daily dosed immunomodulator with minimal adverse effects and the ability to reduce disease progression based on the changes seen in the surrogate markers. Ongoing investigation into combination therapy with interferon beta and glatiramer acetate seeks to demonstrate improved disease control and clinical outcomes.

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