

If you have a fever or rash with any of the above symptoms, stop taking teriflunomide tablets and call your doctor right away.

- **numbness or tingling in your hands or feet that is different from your MS symptoms.** You have a higher chance of getting these symptoms if you:
 - are over 60 years of age
 - take certain medicines that affect your nervous system
 - have diabetes

Tell your doctor if you have numbness or tingling in your hands or feet that is different from your MS.

- **high blood pressure.** Your doctor should check your blood pressure before you start taking teriflunomide tablets and while you are taking teriflunomide tablets.
- **new or worsening breathing problems.** These may be serious and lead to death. Call your doctor right away or get emergency medical help if you have shortness of breath or coughing with or without fever.

The most common side effects of teriflunomide tablets include:

- headache
- diarrhea
- nausea
- hair thinning or loss (alopecia)
- increases in the results of blood tests to check your liver function

These are not all the possible side effects of teriflunomide tablets. For more information, ask your doctor or pharmacist.

Call your doctor right away or get emergency medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store teriflunomide tablets?

- Store teriflunomide tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep teriflunomide tablets and all medicines out of the reach of children.

General information about the safe and effective use of teriflunomide tablets. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use teriflunomide tablets for a condition for which it was not prescribed. Do not give teriflunomide tablets to other people, even if they have the same symptoms you have. They may harm them.

You can ask your doctor or pharmacist for information about teriflunomide tablets that is written for health professionals.

What are the ingredients in teriflunomide tablets?

Active ingredient: teriflunomide

Inactive ingredients in 7 mg and 14 mg tablets: colloidal silicon dioxide, corn starch, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate. The film coating includes hypromellose, polyethylene glycol, talc, titanium dioxide, and yellow iron oxide (for 7 mg).

For more information, call Annora Pharma Private Limited at 1-866-495-1995.



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This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Data

Human data
Available human data are limited. Prospectively reported data from clinical trials and postmarketing reports from > 150 pregnancies in patients treated with teriflunomide and > 300 pregnancies in patients treated with iflunomide have not demonstrated an increased rate of congenital malformations or miscarriage following teriflunomide exposure in the early first trimester when followed by an accelerated elimination procedure. Specific patterns of major congenital malformations in humans have not been observed. Limitations of these data include an inadequate number of reported pregnancies from which to draw conclusions, the short duration of drug exposure in reported pregnancies, which precludes a full evaluation of the fetal risks, incomplete reporting, and the inability to control for confounders (such as underlying maternal disease and use of concomitant medications).

Animal data

When teriflunomide (oral doses of 1, 3, or 10 mg/kg/day) was administered to pregnant rats throughout the period of organogenesis, high incidences of fetal malformation (primarily craniofacial, and axial and appendicular skeletal defects) and fetal death were observed at doses not associated with maternal toxicity. Adverse effects on fetal development were observed following dosing at various stages throughout organogenesis. Maternal plasma exposure at the no-effect level (1 mg/kg/day) for fetal developmental toxicity in rats was less than that in humans at the maximum recommended human dose (MRHD, 14 mg/day).

Administration of teriflunomide (oral doses of 1, 3.5, or 12 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in high incidences of fetal malformation (primarily craniofacial, and axial and appendicular skeletal defects) and fetal death at doses associated with minimal maternal toxicity. Maternal plasma exposure at the no-effect dose (1 mg/kg/day) for fetal developmental toxicity in rabbits was less than that in humans at the MRHD.

In studies in which teriflunomide (oral doses of 0.05, 0.1, 0.3, 0.6, or 1 mg/kg/day) was administered to rats during gestation and lactation, decreased pup survival, and high incidences of malformation (limb defects) and postnatal death were observed in the offspring at doses not associated with maternal toxicity. Maternal plasma exposure at the no-effect dose for prenatal and postnatal developmental toxicity in rats (0.10 mg/kg/day) was less than that in humans at the MRHD.

In animal reproduction studies of malformations, embryofetality and teratogenic effects were observed in pregnant rat and rabbit at or below clinically relevant plasma teriflunomide exposures (AUC). In published reproduction studies in pregnant mice, iflunomide was embryofetal and increased the incidence of malformations (craniofacial, axial skeletal, heart and great vessel). Supplementation with exogenous uridine reduced the teratogenic effects in pregnant mice, suggesting that the mode of action (inhibition of mitochondrial enzyme dihydroorotate dehydrogenase) is the same for therapeutic efficacy and developmental toxicity.

At recommended doses in humans, teriflunomide and iflunomide result in a similar range of plasma concentrations of teriflunomide.

8.2 Lactation

Risk Summary

There are no data on the presence of teriflunomide in human milk, the effects on the breastfed infant, or the effects on milk production. Teriflunomide was detected in rat milk following a single oral dose. Because of the potential for adverse reactions in a breastfed infant from teriflunomide, women should not breastfeed during treatment with teriflunomide.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Exclude pregnancy prior to initiation of treatment with teriflunomide in females of reproductive potential. Advise females to notify their healthcare provider immediately if pregnancy occurs or is suspected during treatment (see *Warnings and Precautions* (5.2, 5.3) and *Use in Specific Populations* (8.1)).

Contraception

Females

Females of reproductive potential should use effective contraception while taking teriflunomide. If teriflunomide is discontinued, use of contraception should be continued until it is verified that plasma concentrations of teriflunomide are less than 0.02 mg/L (0.02 mcg/mL, the level expected to have minimal fetal risk, based on animal data).

Females of reproductive potential who wish to become pregnant should discontinue teriflunomide and undergo an accelerated elimination procedure. Effective contraception should be used until it is verified that plasma concentrations of teriflunomide are less than 0.02 mg/L (0.02 mcg/mL) (see *Warnings and Precautions* (5.2, 5.3) and *Use in Specific Populations* (8.1)).

Males

Teriflunomide is detected in human semen. Animal studies do not specifically evaluate the risk of male-mediated fetal toxicity but have not been conducted. To minimize any possible risk, men not wishing to father a child and their female partners should use effective contraception. Men wishing to father a child should discontinue use of teriflunomide and either undergo an accelerated elimination procedure or wait until verification that the plasma teriflunomide concentration is less than 0.02 mg/L (0.02 mcg/mL) (see *Warnings and Precautions* (5.3)).

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Effectiveness of teriflunomide for the treatment of relapsing form of multiple sclerosis in pediatric patients (10 to 17 years of age) was not established in an adequate and well-controlled clinical study in 168 patients (108 patients received once-daily doses of teriflunomide and 57 patients received placebo) for up to 86 weeks.

Pancreatitis has been reported in adults in the postmarketing setting, but appears to occur at higher frequency in the pediatric population. In this pediatric study, cases of pancreatitis were reported in 1.8% (2/108) of patients who received teriflunomide compared to no patients in the placebo group. All patients in the pediatric trial recovered or were recovering after treatment discontinuation and accelerated elimination procedure (see *Warnings and Precautions* (5.1)).

Additionally, elevated or abnormal blood creatine phosphokinase was reported in 6.4% of pediatric patients who received teriflunomide compared to no patients in the placebo group.

Juvenile Animal Toxicity Data

Oral administration of teriflunomide (0, 0.3, 3, or 6 mg/kg/day) to young rats on postnatal days 21 to 70 resulted in suppression of immune function (T cell dependent antibody response) at the mid and high doses, and adverse effects on male reproductive organs (reduced sperm count and altered neurobehavioral function (increased locomotor activity)) at the high dose. At the no-effect dose (0.3 mg/kg/day) for developmental toxicity in juvenile rats, plasma exposures were less than those in pediatric patients at the doses of teriflunomide tested in the clinical study.

8.5 Geriatric Use

Clinical studies of teriflunomide did not include patients over 65 years old.

8.6 Hepatic Impairment

No dosage adjustment is necessary for patients with mild and moderate hepatic impairment. The pharmacokinetics of teriflunomide in severe hepatic impairment has not been evaluated.

Teriflunomide is contraindicated in patients with severe hepatic impairment (see *Contraindications* (4), *Warnings and Precautions* (5.1), and *Clinical Pharmacology* (12.3)).

8.7 Renal Impairment

No dosage adjustment is necessary for patients with mild, moderate, and severe renal impairment (see *Clinical Pharmacology* (12.3)).

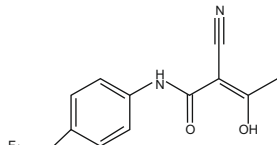
10 OVERDOSEAGE

There is no experience regarding teriflunomide overdose or intoxication in humans. Teriflunomide 70 mg daily up to 14 days was well tolerated by healthy subjects.

In the event of clinically significant overdose or toxicity, cholestyramine or activated charcoal is recommended to accelerate elimination (see *Warnings and Precautions* (5.3)).

11 DESCRIPTION

Teriflunomide is an oral *de novo* pyrimidine synthesis inhibitor of the DHO DH enzyme, with the chemical name (Z)-2-Cyano-3-hydroxybut-2-enoic acid-(4-fluorophenyl)phenyl-amide. Its molecular weight is 270.20, and the molecular formula is C₁₄H₉F₃N₃O, with the following chemical structure:



Teriflunomide is an off white to white powder that is slightly soluble in dimethylformamide.

Teriflunomide is formulated as film coated tablets for oral administration. Teriflunomide tablets contain 7 mg or 14 mg of teriflunomide and the following inactive ingredients: colloidal silicon dioxide, corn starch, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate. The film coating includes hypromellose, polyethylene glycol, talc, titanium dioxide, and yellow iron oxide (for 7 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Teriflunomide, an immunomodulatory agent with anti-inflammatory properties, inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in *de novo* pyrimidine synthesis. The exact mechanism by which teriflunomide exerts its therapeutic effect in multiple sclerosis is unknown but may involve a reduction in the number of activated lymphocytes in CNS.

12.2 Pharmacodynamics

Potential to Prolong the QT Interval

In a placebo-controlled, through QT study performed in healthy adult subjects, there was no evidence that teriflunomide caused QT interval prolongation of clinical significance (i.e., the upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc was below 10 ms).

12.3 Pharmacokinetics

Teriflunomide is the principal active metabolite of iflunomide and is responsible for iflunomide's activity *in vivo*. At recommended doses, teriflunomide and iflunomide result in a similar range of plasma concentrations of teriflunomide.

Based on a population analysis of teriflunomide in healthy adult volunteers and adult MS patients, median *t*_{1/2} was approximately 18 and 19 days after repeated doses of 7 mg and 14 mg respectively. It takes approximately 3 weeks respectively to reach steady state concentrations. The estimated AUC accumulation ratio is approximately 30 after repeated doses of 7 or 14 mg.

Absorption

Median time to reach maximum plasma concentrations is between 1 to 4 hours post dose following oral administration of teriflunomide.

Food does not have a clinically relevant effect on teriflunomide pharmacokinetics.

Distribution

Teriflunomide is extensively bound to plasma protein (> 99%) and is mainly distributed in plasma. The volume of distribution is 11 L after a single intravenous (IV) administration.

Metabolism

Teriflunomide is the major circulating moiety detected in plasma. The primary biotransformation pathway to minor metabolites of teriflunomide is hydrolysis, with oxidation being a minor pathway. Secondary pathways involve oxidation, N-acetylation and sulfate conjugation.

Elimination

Teriflunomide is eliminated mainly through direct biliary excretion of unchanged drug as well as renal excretion of metabolites. Over 21 days, 80.1% of the administered dose is excreted via feces (37.5%) and urine (22.6%). After an accelerated elimination procedure with cholestyramine, an additional 23.1% is recovered (mostly in feces). After a single IV administration, the total body clearance of teriflunomide is 38.5 mL/h.

Drug Interaction Studies

Teriflunomide is not metabolized by Cytochrome P450 or flavin monooxygenase oxidase enzymes.

The potential effect of teriflunomide on other drugs

CYP2C8 substrates

There was an increase in mean repaglinide C_{max} and AUC (1.7- and 2.4 fold, respectively) following repeated doses of teriflunomide and a single dose of 0.25 mg repaglinide, suggesting that teriflunomide is an inhibitor of CYP2C8 *in vivo*. The magnitude of interaction could be higher at the recommended repaglinide dose (see *Drug Interactions* (7)).

CYP1A2 substrates

Repeated doses of teriflunomide decreased mean C_{max} and AUC of caffeine by 18% and 55%, respectively, suggesting that teriflunomide may be a weak inducer of CYP1A2 *in vivo* (see *Drug Interactions* (7)).

DA73 substrates

There was an increase in mean cefaclor C_{max} and AUC (1.43- and 1.54-fold, respectively), following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of organic anion transporter 3 (OAT3) *in vivo* (see *Drug Interactions* (7)).

BCRP and DAT1B1/183 substrates

There was an increase in mean rosvastatin C_{max} and AUC (2.85- and 2.51-fold, respectively) following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of BCRP transporter and organic anion transporting polypeptide 1B1 and 1B3 (DAT1B1/183) (see *Drug Interactions* (7)).

Oral contraceptives

There was an increase in mean ethinylestradiol C_{max} and AUC₀₋₂₄ (1.58- and 1.54-fold, respectively) and levonorgestrel C_{max} and AUC₀₋₂₄ (1.33- and 1.41-fold, respectively) following repeated doses of teriflunomide (see *Drug Interactions* (7)).

Teriflunomide did not affect the pharmacokinetics of bupropion (a CYP2B6 substrate), nifedipine (a CYP3A4 substrate), S-warfarin (a CYP2C9 substrate), omprazole (a CYP2C19 substrate), and metoprolol (a CYP2D6 substrate).

The potential effect of other drugs on teriflunomide

Potent CYP and transporter inducers: Rifampin did not affect the pharmacokinetics of teriflunomide.

Specific Populations

Hepatic impairment

Mild and moderate hepatic impairment had no impact on the pharmacokinetics of teriflunomide. The pharmacokinetics of teriflunomide in severe hepatic impairment has not been evaluated (see *Contraindications* (4), *Warnings and Precautions* (5.1), and *Use in Specific Populations* (8.6)).

Renal impairment

Severe renal impairment had no impact on the pharmacokinetics of teriflunomide (see *Use in Specific Populations* (8.7)).

Gender

In a population analysis, the clearance rate for teriflunomide is 23% less in females than in males.

Race

Effect of race on the pharmacokinetics of teriflunomide cannot be adequately assessed due to a low number of patients who self-identified as Black or African American, Asian, or other races in the clinical trials.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No evidence of carcinogenicity was observed in lifetime carcinogenicity bioassays in mouse and rat. In mouse, teriflunomide was administered orally at doses up to 12 mg/kg/day for up to 95 to 104 weeks; plasma teriflunomide exposures AUC at the highest dose tested are approximately 3 times that in humans at the maximum recommended human dose (MRHD, 14 mg/day). In rat, teriflunomide was administered orally at doses up to 4 mg/kg/day for up to 97 to 104 weeks; plasma teriflunomide AUCs at the highest doses tested are less than that in humans at the MRHD.

Mutagenesis

Teriflunomide was negative in the *in vitro* bacterial reverse mutation (Ames) assay, the *in vitro* HPRT assay, and in *in vivo* micronucleus and chromosomal aberration assays. Teriflunomide was positive in an *in vitro* chromosomal aberration assay in human lymphocytes, with and without metabolic activation. Addition of uridine (to supplement the pyrimidine pool) reduced the magnitude of the clastogenic effect; however, teriflunomide was positive in the *in vitro* chromosomal aberration assay, even in the presence of uridine.

4-TFMA (teriflunomide) (4 TFMA), a minor metabolite of teriflunomide, was positive in the *in vitro* bacterial reverse mutation (Ames) assay, the *in vitro* HPRT assay, and the *in vitro* chromosomal aberration assay in mammalian cells. 4-TFMA was negative in *in vivo* micronucleus and chromosomal aberration assays.

Impairment of Fertility

Oral administration of teriflunomide (0, 1, 3, 10 mg/kg/day) to male rats prior to and during mating (to untreated females) resulted in no adverse effects on fertility; however, reduced epididymal sperm count was observed at the mid and high doses tested. The no-effect dose for reproductive toxicity in male rats (1 mg/kg) is less than the MRHD on a mg/m² basis.

Oral administration of teriflunomide (0, 0.84, 2.8, 8.6 mg/kg/day) to female rats, prior to and during mating (to untreated males) and continuing to gestation day 6, resulted in embryofetality, reduced fetal body weight, and/or malformations at all doses tested. Due to marked embryofetality at the highest doses tested, no fetuses were available for evaluation. The lowest dose tested is less than the MRHD on a mg/m² basis.

14 CLINICAL STUDIES

Four randomized, controlled, double-blind clinical trials established the efficacy of teriflunomide in patients with relapsing forms of multiple sclerosis.

Study 1 was a double-blind, placebo-controlled clinical trial that evaluated once daily doses of teriflunomide tablet 7 mg and teriflunomide tablet 14 mg for up to 26 months in patients with relapsing forms of multiple sclerosis. Patients were required to have a diagnosis of multiple sclerosis exhibiting a relapsing clinical course, with or without progression, and to have experienced at least one relapse over the year preceding the trial or at least two relapses over the two years preceding the trial. Patients were required not to have received interferon-beta for at least four months, or any other multiple sclerosis medication for at least six months before entering the study, nor were these medications permitted during the study. Neurological evaluations were to be performed at screening, every 12 weeks until week 108, and after suspected relapses. MRI was to be performed at screening, and at weeks 24, 48, 72, and 108. The primary endpoint was the annualized relapse rate (ARR).

In Study 1, 1108 patients were randomized to receive teriflunomide 7 mg (n=568), teriflunomide 14 mg (n=568), or placebo (n=363). At entry, patients had an Expanded Disability Status Scale (EDSS) score ≤ 5.5. Patients had a mean age of 38 years, mean disease duration of 5 years, and mean EDSS at baseline of 2.7. A total of 91% of patients had relapsing remitting multiple sclerosis, and 9% had a progressive form of multiple sclerosis with relapses. The mean duration of treatment was 635, 627, and 631 days for teriflunomide 7 mg, teriflunomide 14 mg, and placebo, respectively. The percentage of patients who completed the study treatment period was 75%, 73%, and 71% for teriflunomide 7 mg, teriflunomide 14 mg, and placebo, respectively.

There was a statistically significant reduction in ARR for patients who received teriflunomide 7 mg or teriflunomide 14 mg, compared to patients who received placebo (see Table 2). There was a consistent reduction of the ARR noted in subgroups defined by sex, age group, prior multiple sclerosis therapy, and baseline disease activity.

There was a statistically significant reduction in the relative risk of disability progression at week 108 sustained for 12 weeks (as measured by at least a 1-point increase from baseline EDSS ≤ 5.5 or a 0.5 point increase for those with a baseline EDSS > 5.5) in the teriflunomide 14 mg group compared to placebo (see Table 2 and Figure 1).

The effect of teriflunomide on several magnetic resonance imaging (MRI) variables, including the total lesion volume of T2 and hypointense T1 lesions, was assessed in Study 1. The change in total lesion volume from baseline was significantly lower in the teriflunomide 7 mg and teriflunomide 14 mg groups than in the placebo group. Patients in both teriflunomide groups had significantly fewer gadolinium-enhancing lesions per T1-weighted scan than those in the placebo group (see Table 2).

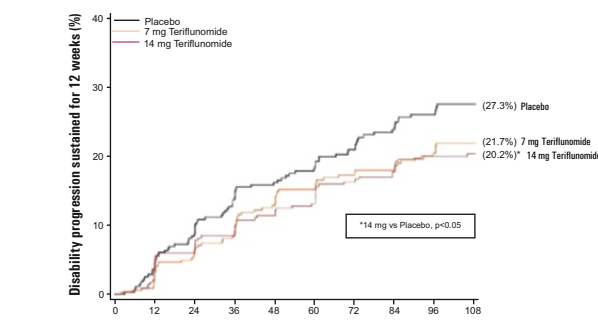
Table 2: Clinical and MRI Results of Study 1

	Teriflunomide 7 mg N=365	Teriflunomide 14 mg N=358	Placebo N=363
Clinical Endpoints			
Annualized relapse rate	0.370 (p=0.0002)	0.369 (p=0.0005)	0.539
Relative risk reduction	31%	31%	-
Percent of patients remaining relapse-free at week 108	53.7%	56.5%	45.6%
Percent disability progression at week 108	21.7% (p=0.0084)	20.2% (p=0.0228)	27.3%
Hazard ratio	0.76	0.70	-
MRI Endpoints			
Median change from baseline in Total lesion volume* (mL) at week 108	0.755 (p=0.0317)	0.345 (p=0.0003)	1.127
Mean number of Gd enhancing T1 lesions per scan	0.570 (p<0.0001)	0.281 (p<0.0001)	1.331

Total lesion volume: sum of T2 and hypointense T1 lesion volume in mL

*p-values based on cubic root transformed data for total lesion volume

Figure 1: Kaplan-Meier Plot of Time to Disability Progression Sustained for 12 Weeks (Study 1)



Number at Risk	Weeks
Placebo	363 338 308 278 258 242 224 211 200 180
7 mg Teriflunomide	365 343 308 280 266 252 238 224 224 178
14 mg Teriflunomide	358 329 302 285 262 251 234 227 217 175

Study 2 was a double-blind, placebo-controlled clinical trial that evaluated once daily doses of teriflunomide 7 mg and teriflunomide 14 mg for up to 40 months in patients with relapsing forms of multiple sclerosis. Patients were required to have a diagnosis of multiple sclerosis exhibiting a relapsing clinical course and to have experienced at least one relapse over the year preceding the trial, or at least three months before entering the trial, nor were these medications permitted during the trial. Neurological evaluations were to be performed at screening, every 12 weeks until completion, and after every suspected relapse. The primary end point was the ARR.

A total of 1185 patients received teriflunomide 7 mg (n=607), teriflunomide 14 mg (n=570), or placebo (n=388). Patients had a mean age of 38 years, a mean disease duration of 5 years, and a mean EDSS at baseline of 2.7. A total of 98% of patients had relapsing remitting multiple sclerosis, and 2% had a progressive form of multiple sclerosis with relapses. The mean duration of treatment was 552, 567, and 571 days for teriflunomide 7 mg, teriflunomide 14 mg, and placebo, respectively. The percentage of patients who completed the study treatment period was 67%, 65%, and 65% for teriflunomide 7 mg, teriflunomide 14 mg, and placebo, respectively.

There was a statistically significant reduction in the ARR for patients who received teriflunomide 7 mg or teriflunomide 14 mg compared to patients who received placebo (see Table 3). There was a consistent reduction of the ARR noted in subgroups defined by sex, age group, prior multiple sclerosis therapy, and baseline disease activity.

There was a statistically significant reduction in the relative risk of disability progression at week 108 sustained for 12 weeks (as measured by at least a 1-point increase from baseline EDSS ≤ 5.5 or a 0.5 point increase for those with a baseline EDSS > 5.5) in the teriflunomide 14 mg group compared to placebo (see Table 3 and Figure 2).

Table 3: Clinical Results of Study 2

	Teriflunomide 7 mg N=407	Teriflunomide 14 mg N=370	Placebo N=388
Clinical Endpoints			
Annualized relapse rate	0.389 (p=0.00183)	0.319 (p=0.0001)	0.501
Relative risk reduction	22%	36%	-
Percent of patients remaining relapse-free at week 108	58.2%	57.1%	46.8%
Percent disability progression at week 108	21.1%	15.6% (p=0.0044)	19.7%
Hazard ratio	0.98	0.69	-