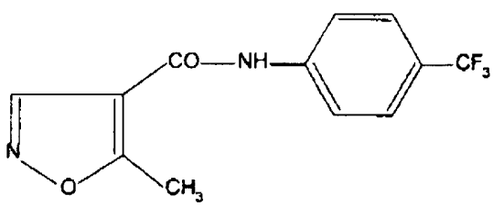
CONTRAINDICATIONS AND WARNINGS

PREGNANCY MUST BE EXCLUDED BEFORE THE START OF TREATMENT WITH ARAVA. ARAVA IS CONTRAINDICATED IN PREGNANT WOMEN, OR WOMEN OF CHILDBEARING POTENTIAL WHO ARE NOT USING RELIABLE CONTRACEPTION. (SEE CONTRAINDICATIONS AND WARNINGS.) PREGNANCY MUST BE AVOIDED DURING ARAVA TREATMENT OR PRIOR TO THE COMPLETION OF THE DRUG ELIMINATION PROCEDURE AFTER ARAVA TREATMENT.

ARAVA™ Tablets (leflunomide) 10 mg, 20 mg, 100 mg

DESCRIPTION

ARAVA™ (leflunomide) is a pyrimidine synthesis inhibitor. The chemical name for leflunomide is N-(4'-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide. It has an empirical formula $C_{12}H_9F_3N_2O_2$, a molecular weight of 270.2 and the following structural formula:



ARAVA is available for oral administration as tablets containing 10, 20, or 100 mg of active drug. Combined with leflunomide are the following inactive ingredients: colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, polyethylene glycol, povidone, starch, talc, titanium dioxide, and yellow ferric oxide (20 mg tablet only).

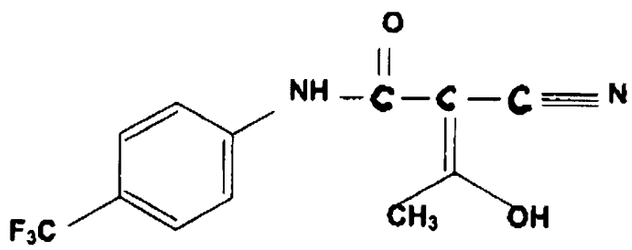
CLINICAL PHARMACOLOGY

Mechanism Of Action

Leflunomide is an isoxazole immunomodulatory agent which inhibits dihydroorotate dehydrogenase (an enzyme involved in de novo pyrimidine synthesis) and has antiproliferative activity. Several *in vivo* and *in vitro* experimental models have demonstrated an anti-inflammatory effect.

Pharmacokinetics

Following oral administration, leflunomide is metabolized to an active metabolite A77 1726 (hereafter referred to as M1) which is responsible for essentially all of its activity *in vivo*. Plasma levels of leflunomide are occasionally seen, at very low levels. Studies of the pharmacokinetics of leflunomide have primarily examined the plasma concentrations of this active metabolite.



Absorption

Following oral administration, peak levels of the active metabolite, M1, occurred between 6-12 hours after dosing. Due to the very long half-life of M1 (~2 weeks), a loading dose of 100 mg for 3 days was used in clinical studies to facilitate the rapid attainment of steady-state levels of M1. Without a loading dose, it is estimated that attainment of steady-state plasma concentrations would require nearly two months of dosing. The resulting plasma concentrations following both loading doses and continued clinical dosing indicate that M1 plasma levels are dose proportional.

Table 1. Pharmacokinetic Parameters for M1 after Administration of Leflunomide at Doses of 5, 10, and 25 mg/day for 24 Days to Patients with Rheumatoid Arthritis (Mean ± SD) (Study YU204)

Maintenance (Loading) Dose

Parameter	5 mg (50 mg)	10 mg (100 mg)	25 mg (100 mg)
C_{24} (Day 1) (μg/mL)[1]	4.0 ± 0.6	8.4 ± 2.1	8.5 ± 2.2
C_{24} (ss) (μg/mL)[2]	8.8 ± 2.9	18 ± 9.6	63 ± 36
t ½ (DAYS)	15 ± 3	14 ± 5	18 ± 9

[1] Concentration at 24 hours after loading dose

[2] Concentration at 24 hours after maintenance doses at steady state

Relative to an oral solution, ARAVA tablets are 80% bioavailable. Co-administration of leflunomide tablets with a high fat meal did not have a significant impact on M1 plasma levels.

Distribution

M1 has a low volume of distribution (Vss = 0.13 L/kg) and is extensively bound (>99.3%) to albumin in healthy subjects. Protein binding has been shown to be linear at therapeutic concentrations. The free fraction of M1 is slightly higher in patients with rheumatoid arthritis and approximately doubled in patients with chronic renal failure; the mechanism and significance of these increases are unknown.

Metabolism

Leflunomide is metabolized to one primary (M1) and many minor metabolites. Of these minor metabolites, only 4-trifluoromethylaniline (TFMA) is quantifiable, occurring at low levels in the plasma of some patients. The parent compound is rarely detectable in plasma. At the present time the specific site of leflunomide metabolism is unknown. *In vivo* and *in vitro* studies suggest a role for both the GI wall and the liver in drug metabolism. No specific enzyme has been identified as the primary route of metabolism for leflunomide; however, hepatic cytosolic and microsomal cellular fractions have been identified as sites of drug metabolism.

Elimination

The active metabolite M1 is eliminated by further metabolism and subsequent renal excretion as well as by direct biliary excretion. In a 28 day study of drug elimination (n=3) using a single dose of radiolabeled compound, approximately 43% of the total radioactivity was eliminated in the urine and 48% was eliminated in the feces. Subsequent analysis of the samples revealed the primary urinary metabolites to be leflunomide glucuronides and an oxanilic acid derivative of M1. The primary fecal metabolite was M1. Of these two routes of elimination, renal elimination is more significant over the first 96 hours after which fecal elimination begins to predominate. In a study involving the intravenous administration of M1, the clearance was estimated to be 31mL/hr.

In small studies using activated charcoal (n=1) or cholestyramine (n=3) to facilitate drug elimination, the *in vivo* plasma half-life of M1 was reduced from >1 week to approximately 1 day (see OVERDOSAGE). Similar reductions in plasma half-life were observed for a series of volunteers (n=96) enrolled in pharmacokinetic trials who were given cholestyramine. This suggests that biliary recycling is a major contributor to the long elimination half-life of M1. Studies with both hemodialysis and CAPD (chronic ambulatory peritoneal dialysis) indicate that M1 is not dialyzable.

Special Populations

Age and Gender

Neither age nor gender have been shown to cause a consistent change in the *in vivo* pharmacokinetics of M1.

Smoking

A population based pharmacokinetic analysis of the phase III data indicates that smokers have a 38% increase in clearance over non-smokers; however, no difference in clinical efficacy was seen between smokers and nonsmokers.

Chronic Renal Insufficiency

In single dose studies in patients (n=6) with chronic renal insufficiency requiring either chronic ambulatory peritoneal dialysis (CAPD) or hemodialysis, neither had a significant impact on circulating levels of M1. The

free fraction of M1 was almost doubled, but the mechanism of this increase is not known. In light of the fact that the kidney plays a role in drug elimination, and without adequate studies of leflunomide use in subjects with renal insufficiency, caution should be used when ARAVA is administered to these patients.

Hepatic Insufficiency

Studies of the effect of hepatic insufficiency on M1 pharmacokinetics have not been done. Given the need to metabolize leflunomide into the active species, the role of the liver in drug elimination/recycling, and the possible risk of increased hepatic toxicity, the use of leflunomide in patients with hepatic insufficiency is not recommended.

Drug Interactions

In vivo drug interaction studies have demonstrated a lack of a significant drug interaction between leflunomide and tri-phasic oral contraceptives, and cimetidine.

In vitro studies of protein binding indicated that warfarin did not affect M1 protein binding. At the same time M1 was shown to cause increases ranging from 13-50% in the free fraction of diclofenac, ibuprofen and tolbutamide at concentrations in the clinical range. *In vitro* studies of drug metabolism indicate that M1 inhibits CYP 450 2C9, which is responsible for the metabolism of many NSAIDs. M1 has been shown to inhibit the formation of 4'-hydroxydiclofenac from diclofenac *in vitro*. The clinical significance of these findings is unknown, however, there was extensive concomitant use of NSAIDs in clinical studies and no differential effect was observed.

Methotrexate

Coadministration, in 30 patients, of ARAVA (100 mg/day x 2 days followed by 10 - 20 mg/day) with methotrexate (10 - 25 mg/week, with folate) demonstrated no pharmacokinetic interaction between the two drugs. However, co-administration increased risk of hepatotoxicity (see PRECAUTIONS - **Drug Interactions**-Hepatotoxic Drugs).

Rifampin

Following concomitant administration of a single dose of ARAVA to subjects receiving multiple doses of

rifampin, M1 peak levels were increased (~40%) over those seen when ARAVA was given alone. Because of the potential for ARAVA levels to continue to increase with multiple dosing, caution should be used if patients are to receive both ARAVA and rifampin.

CLINICAL STUDIES

The efficacy of ARAVA in the treatment of rheumatoid arthritis (RA) was demonstrated in three controlled trials. Relief of signs and symptoms was assessed using the ACR20 Responder Index, a composite of clinical, laboratory, and functional measures in rheumatoid arthritis. An "ACR20 Responder" is a patient who had ≥ 20% improvement in both tender and swollen joint counts and in 3 of the following 5 criteria: physician global assessment, patient global assessment, function/disability measure (Modified Health Assessment Questionnaire), visual analog pain scale, and erythrocyte sedimentation rate or C-reactive protein. An "ACR20 Responder at Endpoint" is a patient who completed the study and was an ACR20 Responder at the completion of the study. Retardation of structural damage compared to control was assessed using the Sharp Score (Sharp, JT, Scoring Radiographic Abnormalities in Rheumatoid Arthritis, Radiologic Clinics of North America, 1996; vol. 34, pgs. 233-241), a composite score of erosions and joint space narrowing in hands/wrists and forefeet.

All leflunomide patients used an initial loading dose of 100 mg/day for 3 days.

Study US301 randomized 482 subjects with active RA of at least 6 months duration to leflunomide 20 mg/day (n=182), methotrexate 7.5 mg/week increasing to 15 mg/week (n=182), or placebo (n=118). All patients received folate 1mg BID. Treatment duration was 52 weeks.

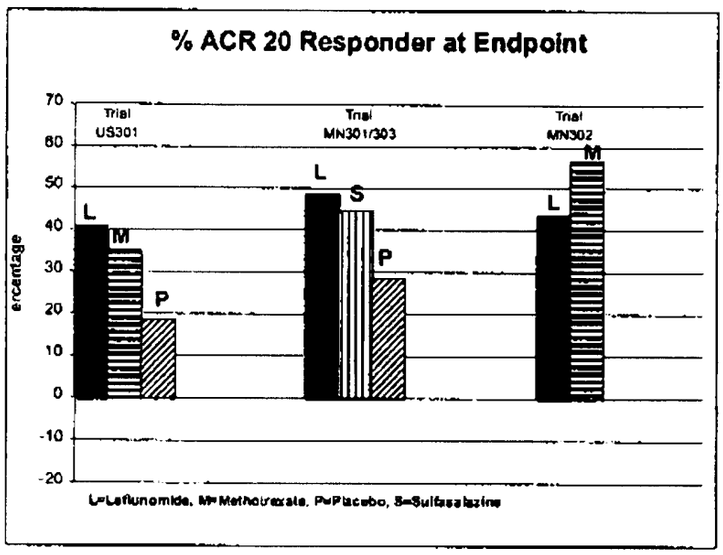
Study MN301 randomized 358 subjects with active RA to leflunomide 20 mg/day (n=133), sulfasalazine 2.0 g/day (n=133), or placebo (n=92). Treatment duration was 24 weeks. Study MN303 was an optional 6-month blinded continuation of MN301 without the placebo arm, resulting in a 12-month comparison of leflunomide and sulfasalazine.

Study MN302 randomized 999 subjects with active RA to leflunomide 20 mg/day (n=501) or methotrexate at 7.5 mg/week increasing to 15 mg/week (n=498). Folate supplementation was used in 10% of patients. Treatment duration was 52 weeks.

Clinical Trial Data

The ACR20 Responder at Endpoint rates are shown in Figure 1. ARAVA was statistically significantly superior to placebo in reducing the signs and symptoms of RA by the primary efficacy analysis, ACR20 Responder at Endpoint. ACR20 Responder at Endpoint rates with ARAVA treatment were consistent across the 6 and 12 month studies (41-49%). No consistent differences were demonstrated between leflunomide and methotrexate or between leflunomide and sulfasalazine. ARAVA treatment effect was evident by 1 month, stabilized by 3-6 months, and continued throughout the course of treatment as shown in Figure 2.

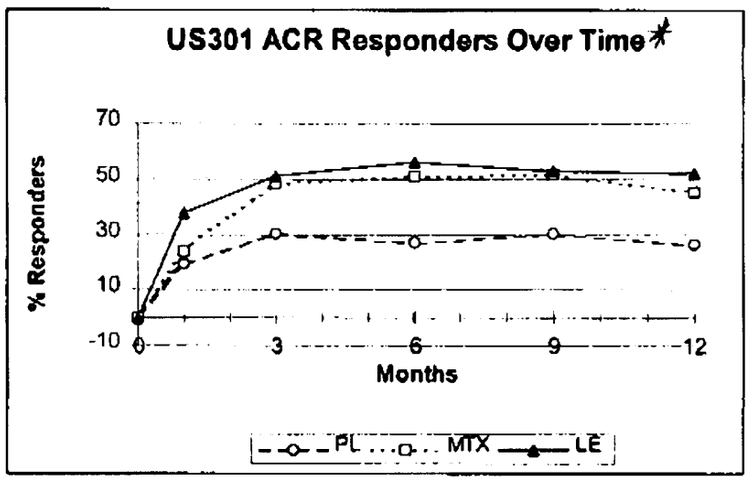
Figure 1: % ACR20 responder at endpoint



	Comparisons	95% Confidence Interval	p Value
US301	Leflunomide vs. Placebo	(12, 32)	<0.0001
	Methotrexate vs. Placebo	(8, 30)	<0.0001
	Leflunomide vs. Methotrexate	(-4, 16)	NS
MN301	Leflunomide vs. Placebo	(7, 33)	0.0026
	Sulfasalazine vs. Placebo	(4, 29)	0.0121

	Leflunomide vs. Sulfasalazine	(-8, 16)	NS
MN302	Leflunomide vs. Methotrexate	(-19, -7)	<0.0001

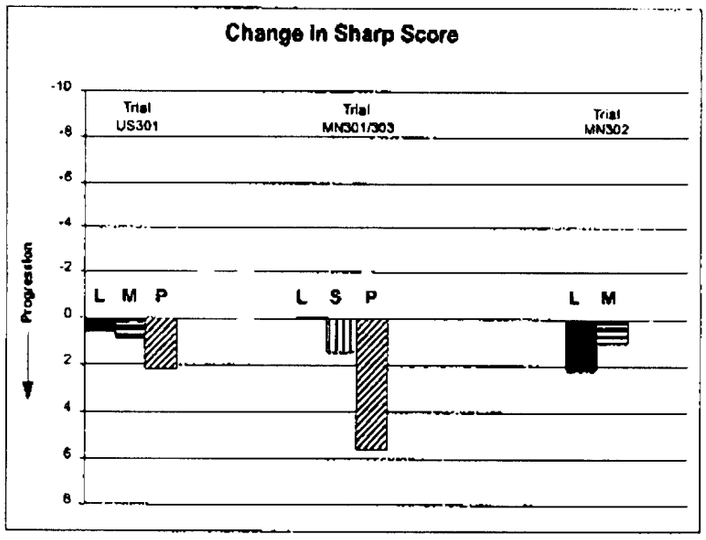
Figure 2



* Last Observation Carried Forward.

The change from baseline to endpoint in progression of structural disease, as measured by the Sharp X-ray score, is displayed in Figure 3. ARAVA was statistically significantly superior to placebo in reducing the progression of disease by the Sharp Score. No consistent differences were demonstrated between leflunomide and methotrexate or between leflunomide and sulfasalazine.

Figure 3: Change In Sharp Scores



Comparisons		95% Confidence Interval	p Value
US301	Leflunomide vs. Placebo	(-4.0, -1.1)	0.0007
	Methotrexate vs. Placebo	~~(0.2, 2.6)~~ (-2.6, -0.2)	0.0187
	Leflunomide vs. Methotrexate	(-2.3, 0.0)	0.0494
MN301	Leflunomide vs. Placebo	(-9.0, -1.4)	0.0081
	Sulfasalazine vs. Placebo	(-7.7, 0.0)	NS
	Leflunomide vs. Sulfasalazine	(-5.4, 2.3)	NS
MN302	Leflunomide vs. Methotrexate	(-2.7, 8.0)	NS

← please verify / correct if necessary

INDICATIONS AND USAGE

ARAVA is indicated in adults for the treatment of active rheumatoid arthritis (RA) to reduce signs and symptoms and to retard structural damage as evidenced by X-ray erosions and joint space narrowing (See CLINICAL STUDIES).

Aspirin, nonsteroidal anti-inflammatory agents and/or low dose corticosteroids may be continued during treatment with ARAVA (see PRECAUTIONS - **Drug Interactions** - NSAIDs). The combined use of ARAVA with antimalarials, intramuscular or oral gold, D penicillamine, azathioprine, or methotrexate has not been adequately studied.

CONTRAINDICATIONS

ARAVA is contraindicated in patients with known hypersensitivity to leflunomide or any of the other components of ARAVA.

ARAVA can cause fetal harm when administered to a pregnant woman. Leflunomide, when administered orally to rats during organogenesis at a dose of 15 mg/kg, was teratogenic (most notably anophthalmia or microophthalmia and internal hydrocephalus). The systemic exposure of rats at this dose was approximately 1/10 the human exposure level based on AUC. Under these exposure conditions, leflunomide also caused a decrease in the maternal body weight and an increase in embryolethality with a decrease in fetal body weight for surviving fetuses. In rabbits, oral treatment with 10 mg/kg of leflunomide during organogenesis resulted in fused, dysplastic sternebrae. The exposure level at this dose was essentially equivalent to the maximum human exposure level based on AUC. At a 1 mg/kg dose, leflunomide was not teratogenic in rats and rabbits.

When female rats were treated with 1.25 mg/kg of leflunomide beginning 14 days before mating and continuing until the end of lactation, the offspring exhibited marked (greater than 90%) decreases in postnatal survival. The systemic exposure level at 1.25 mg/kg was approximately 1/100 the human exposure level based on AUC.

ARAVA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

WARNINGS

Hepatotoxicity

In clinical trials, ARAVA treatment was associated with elevations of liver enzymes, primarily ALT and AST, in a significant number of patients; these effects were generally reversible. Most transaminase elevations were mild (≤2-fold ULN) and usually resolved while continuing treatment. Marked elevations (>3-fold ULN) occurred infrequently and reversed with dose reduction or discontinuation of treatment. The following table shows liver enzyme elevations seen with monthly monitoring in clinical trials US301 and MN301. It was notable that the absence of folate use in MN302 was associated with a considerably greater incidence of liver enzyme elevation on methotrexate.

Table 2. Elevations > 3x Upper Limits of Normal (ULN)

	US301			MN301			MN302*	
	LEF	PL	MTX	LEF	PL	SSZ	LEF	MTX
ALT (SGPT)								
> 3x ULN (n %)	8 (4.4)	3 (2.5)	5 (2.7)	2 (1.5)	1 (1.1)	2 (1.5)	13 (2.6)	83 (16.7)
Reversed to ≤ 2x ULN:	8	3	5	2	1	2	12	82
Timing of Elevation								
0-3 Months	6	1	1	2	1	2	7	27
4-6 Months	1	1	3	-	-	-	1	34
7-9 Months	1	1	1	-	-	-	-	16
10-12 Months	-	-	-	-	-	-	5	6
AST (SGOT)								
> 3x ULN (n %)	4 (2.2)	2 (1.7)	1 (0.6)	2 (1.5)	0 -	5 (3.8)	7 (1.4)	29 (5.8)
Reversed to ≤ 2x ULN	4	2	1	2	-	4	5	29
Timing of Elevation								
0-3 Months	2	1	-	2	-	4	3	10
4-6 Months	1	1	1	-	-	1	1	11
7-9 Months	1	-	-	-	-	-	-	8
10-12 Months	-	-	-	-	-	-	3	-

*Only 10% of patients in MN302 received folate. All patients in US301 received folate.

At minimum, ALT (SGPT) should be performed at baseline and monitored initially at monthly intervals then, if stable, at intervals determined by the individual clinical situation.

Guidelines for dose adjustment or discontinuation based on the severity and persistence of ALT elevation are recommended as follows: For confirmed ALT elevations >2-fold ULN, dose reduction to 10 mg/day may allow continued administration of ARAVA. If elevations >2 but ≤3-fold ULN persist despite dose reduction, liver biopsy is recommended if continued treatment is desired. If elevations >3-fold ULN persist despite cholestyramine administration (see OVERDOSAGE) and dose reduction, ARAVA should be discontinued and cholestyramine should be re-administered with close monitoring and retreatment with cholestyramine as indicated.

Rare elevations of alkaline phosphatase and bilirubin have been observed. Trial US301 used ACR Methotrexate Liver Biopsy Guidelines for monitoring therapy. One of 182 patients receiving leflunomide and 1 of 182 patients receiving methotrexate underwent liver biopsy at 106 and 50 weeks respectively. The biopsy for the leflunomide subject was Roegnik Grade IIIA and for the methotrexate subject, Roegnik Grade I.

Pre-existing Hepatic Disease

Given the possible risk of increased hepatotoxicity, and the role of the liver in drug activation, elimination and recycling, the use of ARAVA is not recommended in patients with significant hepatic impairment or positive Hepatitis B or C serologies.

Malignancy

The risk of malignancy, particularly lymphoproliferative disorders, is increased with the use of some immunosuppression medications. There is a potential for immunosuppresion with ARAVA. No apparent increase in the incidence of malignancies and lymphoproliferative disorders was reported in the clinical trials of ARAVA, but larger and longer-term studies would be needed to determine whether there is an increased risk of malignancy or lymphoproliferative disorders with ARAVA.

Use in Women of Childbearing Potential

There are no adequate and well-controlled studies evaluating ARAVA in pregnant women. However, based on animal studies, leflunomide may increase the risk of fetal death or teratogenic effects when administered to a pregnant woman (see CONTRAINDICATIONS). Women of childbearing potential must not be started on ARAVA until pregnancy is excluded and it has been confirmed that they are using reliable contraception. Before starting treatment with ARAVA, patients must be fully counseled on the potential for serious risk to the fetus.

The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must notify the physician immediately for pregnancy testing and, if positive, the physician and patient must discuss the risk to the pregnancy. It is possible that rapidly lowering the blood level of the active metabolite by instituting the drug elimination procedure described below at the first delay of menses may decrease the risk to the fetus from ARAVA.

Upon discontinuing ARAVA, it is recommended that all women of childbearing potential undergo the drug elimination procedure described below. Women receiving ARAVA treatment who wish to become pregnant must discontinue ARAVA and undergo the drug elimination procedure described below which includes verification of M1 metabolite plasma levels less than 0.02mg/L (0.02µg/mL). Human plasma levels of the active metabolite (M1) less than 0.02 mg/L (0.02 µg/mL) are expected to have minimal risk based on available animal data.

Drug Elimination Procedure

The following drug elimination procedure is recommended to achieve non-detectable plasma levels (less than 0.02 mg/L or 0.02 µg/mL) after stopping treatment with ARAVA:

1) Administer cholestyramine 8 grams 3 times daily for 11 days. (The 11 days do not need to be consecutive unless there is a need to lower the plasma level rapidly.)
2) Verify plasma levels less than 0.02mg/L (0.02 g/mL) by two separate tests at least 14 days apart. If plasma levels are higher than 0.02mg/L, additional cholestyramine treatment should be considered.

Without the drug elimination procedure, it may take up to 2 years to reach plasma M1 metabolite levels less than 0.02mg/L due to individual variation in drug clearance.

PRECAUTIONS

General

Renal Insufficiency

Single dose studies in dialysis patients show a doubling of the free fraction of M1 in plasma. There is no clinical experience in the use of ARAVA in patients with renal impairment. Caution should be used when administering this drug in this population.

Immunosuppression Potential

Although there is no clinical experience in the following patient populations, ARAVA is not recommended for patients with severe immunodeficiency, bone marrow dysplasia, or severe, uncontrolled infections because of the theoretical potential for immunosuppression.

No clinical data are available on the efficacy and safety of vaccinations during ARAVA treatment. Vaccination with live vaccines is, however, not recommended. The long half-life of ARAVA should be considered when contemplating administration of a live vaccine after stopping ARAVA.

Information for Patients

The potential for increased risk of birth defects should be discussed with female patients of childbearing potential. It is recommended that physicians advise women that they may be at increased risk of having a child with birth defects if they are pregnant when taking ARAVA, become pregnant while taking ARAVA, or do not wait to become pregnant until they have stopped taking ARAVA and followed the drug elimination procedure.

Laboratory Tests

At minimum, ALT (SGPT) should be performed at baseline and monitored initially at monthly intervals then, if stable, at intervals determined by the individual clinical situation.

Due to a specific effect on the brush border of the renal proximal tubule, ARAVA has a uricosuric effect. A separate effect of hypophosphaturia is seen in some patients. These effects have not been seen together, nor have there been alterations in renal function.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No evidence of carcinogenicity was observed in a 2-year bioassay in rats at oral doses of leflunomide up to the maximally tolerated dose of 6 mg/kg (approximately 1/40 the maximum human M1 systemic exposure based on AUC). However, male mice in a 2-year bioassay exhibited an increased incidence in lymphoma at an oral dose of 15 mg/kg, the highest dose studied (1.7 times the human M1 exposure based on AUC). Female mice, in the same study, exhibited a dose-related increased incidence of bronchoalveolar adenomas and carcinomas combined beginning at 1.5 mg/kg (approximately 1/10 the human M1 exposure based on AUC). The significance of the findings in mice relative to the clinical use of ARAVA is not known.

Leflunomide was not mutagenic in the Ames Assay, the Unscheduled DNA Synthesis Assay, or in the HGPRT Gene Mutation Assay. In addition, leflunomide was not clastogenic in the *in vivo* Mouse Micronucleus Assay nor in the *in vivo* Cytogenetic Test in Chinese Hamster Bone Marrow Cells. However,

4-trifluoromethylaniline (TMFA), a minor metabolite of leflunomide, was mutagenic in the Ames Assay and in the HGPRT Gene Mutation Assay, and was clastogenic in the *in vitro* Assay for Chromosome Aberrations in the Chinese Hamster Cells. TFMA was not clastogenic in the *in vivo* Mouse Micronucleus Assay nor in the *in vivo* Cytogenetic Test in Chinese Hamster Bone Marrow Cells.

Leflunomide had no effect on fertility in either male or female rats at oral doses up to 4.0 mg/kg (approximately 1/30 the human M1 exposure based on AUC).

Pregnancy

Pregnancy Category X. See CONTRAINDICATIONS section.

Nursing Mothers

ARAVA should not be used by nursing mothers. It is not known whether ARAVA is excreted in human milk. Many drugs are excreted in human milk, and there is a potential for serious adverse reactions in nursing infants from ARAVA. Therefore, a decision should be made whether to proceed with nursing or to initiate treatment with ARAVA, taking into account the importance of the drug to the mother.

Use In Males

Available information does not suggest that ARAVA would be associated with an increased risk of male-mediated fetal toxicity. However, animal studies to evaluate this specific risk have not been conducted. To minimize any possible risk, men wishing to father a child should consider discontinuing use of ARAVA and taking cholestyramine 8 grams 3 times daily for 11 days.

Drug Interactions

Cholestyramine and Charcoal

Administration of cholestyramine or activated charcoal in patients (n=13) and volunteers (n=96) resulted in a rapid and significant decrease in plasma M1 (the active metabolite of leflunomide) concentration (see OVERDOSAGE).

Hepatotoxic Drugs

Increased side effects may occur when leflunomide is given concomitantly with hepatotoxic substances. This is also to be considered when leflunomide treatment is followed by such drugs without a drug elimination procedure. In a small (n=30) combination study of ARAVA with **methotrexate**, a 2 to 3-fold elevation in liver enzymes was seen in 5 of 30 patients. All elevations resolved, 2 with continuation of both drugs and 3 after discontinuation of leflunomide. A >3-fold increase was seen in another 5 patients. All of these also resolved, 2 with continuation of both drugs and 3 after discontinuation of leflunomide. Three patients met "ACR criteria" for liver biopsy (1:Roegnik grade I, 2:Roegnik grade IIIa). No pharmacokinetic interaction was identified (see Clinical Pharmacology).

NSAIDs

In *in vitro* studies, M1 was shown to cause increases ranging from 13-50% in the free fraction of diclofenac and ibuprofen at concentrations in the clinical range. The clinical significance of this finding is unknown, however, there was extensive concomitant use of NSAIDs in clinical studies and no differential effect was observed.

Tolbutamide

In *in vitro* studies, M1 was shown to cause increases ranging from 13-50% in the free fraction of tolbutamide at concentrations in the clinical range. The clinical significance of this finding is unknown.

Rifampin

Following concomitant administration of a single dose of ARAVA to subjects receiving multiple doses of rifampin, M1 peak levels were increased (~40%) over those seen when ARAVA was given alone. Because of the potential for ARAVA levels to continue to increase with multiple dosing, caution should be used if patients are to be receiving both ARAVA and rifampin.

Pediatric Use

The safety and efficacy of ARAVA in the pediatric population has not been studied. Use of ARAVA in patients less than 18 years of age is not recommended.

Geriatric Use

No dosage adjustment is needed in patients over 65.

ADVERSE REACTIONS

Adverse reactions associated with the use of leflunomide in RA include diarrhea, elevated liver enzymes (ALT and AST), alopecia and rash. In the controlled studies, the following adverse events were reported, regardless of causality. (See Table 3.)

Table 3 Percentage Of Patients With Adverse Events ≥3% In Any Leflunomide Treated Group

	All RA Studies	Placebo-Controlled Trials				Active-Controlled Trials	
		MN 301 and US 301				MN 302*	
	LEF (N= 1339)†	LEF (N=315)	PBO (N=210)	SSZ (N=133)	MTX (N=182)	LEF (N=501)	MTX (N=498)
BODY AS A WHOLE							
Allergic Reaction	2%	5%	2%	0%	6%	1%	2%
Asthenia	3%	6%	4%	5%	6%	3%	3%
Flu Syndrome	2%	4%	2%	0%	7%	0%	0%
Infection	4%	0%	0%	0%	0%	0%	0%
Injury Accident	5%	7%	5%	3%	11%	6%	7%
Pain	2%	4%	2%	2%	5%	1%	<1%
Abdominal Pain	6%	5%	4%	4%	8%	6%	4%
Back Pain	5%	6%	3%	4%	9%	8%	7%
CARDIOVASCULAR							
Hypertension‡	10%	9%	4%	4%	3%	10%	4%
Chest Pain	2%	4%	2%	2%	4%	1%	2%
GASTROINTESTINAL							
Anorexia	3%	3%	2%	5%	2%	3%	3%
Diarrhea	17%	27%	12%	10%	20%	22%	10%
Dyspepsia	5%	10%	10%	9%	13%	6%	7%
Gastroenteritis	3%	1%	1%	0%	6%	3%	3%
Abnormal Liver Enzymes	5%	10%	2%	4%	10%	6%	17%
Nausea	9%	13%	11%	19%	18%	13%	18%
GI/Abdominal Pain	5%	6%	4%	7%	8%	8%	8%
Mouth Ulcer	3%	5%	4%	3%	10%	3%	6%
Vomiting	3%	5%	4%	4%	3%	3%	3%
METABOLIC AND NUTRITIONAL							
Hypokalemia	1%	3%	1%	1%	1%	1%	<1%
Weight Loss	4%	2%	1%	2%	0%	2%	2%

Table 3	Percentage Of Patients With Adverse Events ≥3% In Any Leflunomide Treated Group						
	All RA Studies	Placebo-Controlled Trials				Active-Controlled Trials	
		MN 301 and US 301				MN 302*	
	LEF (N= 1339)[1]	LEF (N=315)	PBO (N=210)	SSZ (N=133)	MTX (N=182)	LEF (N=501)	MTX (N=498)
MUSCULO-SKELETAL SYSTEM							
Arthralgia	1%	4%	3%	0%	9%	<1%	1%
Leg Cramps	1%	4%	2%	2%	6%	0%	0%
Joint Disorder	4%	2%	2%	2%	2%	8%	6%
Synovitis	2%	<1%	1%	0%	2%	4%	2%
Tenosynovitis	3%	2%	0%	1%	2%	5%	1%
NERVOUS SYSTEM							
Dizziness	4%	5%	3%	6%	5%	7%	6%
Headache	7%	13%	11%	12%	21%	10%	8%
Paresthesia	2%	3%	1%	1%	2%	4%	3%
RESPIRATORY SYSTEM							
Bronchitis	7%	5%	2%	4%	7%	8%	7%
Increased Cough	3%	4%	5%	3%	6%	5%	7%
Respiratory Infection	15%	21%	21%	20%	32%	27%	25%
Pharyngitis	3%	2%	1%	2%	1%	3%	3%
Pneumonia	2%	3%	0%	0%	1%	2%	2%
Rhinitis	2%	5%	2%	4%	3%	2%	2%
Sinusitis	2%	5%	5%	0%	10%	1%	1%
SKIN AND APPENDAGES							
Alopecia	10%	9%	1%	6%	6%	17%	10%
Eczema	2%	1%	1%	1%	1%	3%	2%
Pruritis	4%	5%	2%	3%	2%	6%	2%
Rash	10%	12%	7%	11%	9%	11%	10%
Dry Skin	2%	3%	2%	2%	0%	3%	1%
UROGENITAL SYSTEM							
Urinary Tract Infection	5%	5%	7%	4%	2%	5%	6%

*Only 10% of patients in MN302 received folate. All patients in US301 received folate.

[1] Includes all controlled and uncontrolled trials with leflunomide.
[2] Hypertension as a preexisting condition was over represented in all leflunomide treatment groups in phase III trials. Analysis of new onset hypertension revealed no difference among the treatment groups.

In addition, the following adverse events have been reported in 1% to <3% of the RA patients in the leflunomide treatment group in controlled clinical trials.

Body as a Whole: abscess, cyst, fever, hernia, malaise, pain, neck pain, pelvic pain;

Cardiovascular: angina pectoris, migraine, palpitation, tachycardia, vasculitis, vasodilatation, varicose vein;

Gastrointestinal: cholelithiasis, colitis, constipation, esophagitis, flatulence, gastritis, gingivitis, melena, oral moniliasis, pharyngitis, salivary gland enlarged, stomatitis (or aphthous stomatitis), tooth disorder;

Endocrine: diabetes mellitus, hyperthyroidism;

Hemic and Lymphatic System: anemia; (including iron deficiency anemia), ecchymosis;

Metabolic and Nutritional: creatine phosphokinase increased, peripheral edema, hyperglycemia, hyperlipidemia;

Musculo-Skeletal System: arthrosis, bursitis, muscle cramps, myalgia, bone necrosis, bone pain, tendon rupture;

Nervous System: anxiety, depression, dry mouth, insomnia, neuralgia, neuritis, sleep disorder, sweat, vertigo;

Respiratory System: asthma, dyspnea, epistaxis, lung disorder;

Skin and Appendages: acne, contact dermatitis, fungal dermatitis, hair discoloration, hematoma, herpes simplex, herpes zoster, nail disorder, skin nodule, subcutaneous nodule, maculopapular rash, skin disorder, skin discoloration, ulcer skin;

Special Senses: blurred vision, cataract , conjunctivitis, eye disorder, taste perversion;

Urogenital System: albuminuria, cystitis, dysuria, hematuria, menstrual disorder, vaginal moniliasis, prostate disorder, urinary frequency.

Other less common adverse events seen in clinical trials include: 1 case of anaphylactic reaction occured in Phase 2 following rechallenge of drug after withdrawal due to rash (rare); urticaria; eosinophilia; transient thrombocytopenia (rare); and leukopenia <2000G/L (rare). A causal relationship of these events to leflunomide has not been established.

DRUG ABUSE AND DEPENDENCE

ARAVA has no known potential for abuse or dependence.

OVERDOSAGE

There is no human experience regarding leflunomide overdosage. In mouse and rat acute toxicology studies, the minimally toxic dose for oral leflunomide was 200-500 mg/kg and 100 mg/kg, respectively (approximately > 350 times the maximum recommended human dose, respectively).

In the event of a significant overdose or toxicity, cholestyramine or charcoal administration is recommended to accelerate elimination. Cholestyramine given orally at a dose of 8 gm three times a day for 24 hours to three healthy volunteers decreased plasma levels of M1 by approximately 40% in 24 hours and by 49 - 65% in 48 hours.

Administration of activated charcoal (powder made into a suspension) orally or via nasogastric tube (50 gm every 6 hours for 24 hours) has been shown to reduce plasma concentrations of the active metabolite, M1, by 37% in 24 hours and by 48% in 48 hours.

These drug elimination procedures may be repeated if clinically necessary.

DOSAGE AND ADMINISTRATION

Loading Dose

Due to the long half-life in patients with RA and recommended dosing interval (24 hours), a loading dose is needed to provide steady-state concentrations more rapidly. It is recommended that ARAVA therapy be initiated with a loading dose of one 100 mg tablet per day for 3 days.

Maintenance Therapy

Daily dosing of 20 mg is recommended for treatment of patients with RA. A small cohort of patients (n=104), treated with 25 mg/day, experienced a greater incidence of side effects; alopecia, weight loss, liver enzyme elevations. Doses higher than 20 mg/day are not recommended. If dosing at 20 mg/day is not well tolerated clinically, the dose may be decreased to 10 mg daily. Liver enzymes should be monitored and dose adjustments may be necessary (see WARNINGS - Hepatotoxicity). Due to the prolonged half-life of the active metabolite of leflunomide, patients should be carefully observed after dose reduction, since it may take several weeks for metabolite levels to decline.

HOW SUPPLIED

ARAVA Tablets in 10 and 20 mg strengths are packaged in bottles. ARAVA Tablets 100 mg strength are packaged in blister packs.

ARAVA ™ (leflunomide) Tablets			
Strength	**Quantity**	**NDC Number**	**Description**
10 mg	30 count bottle 100 count bottle [redacted]	0088-2160-30 0088-2160-47 [redacted]	White, round film-coated tablet embossed with "ZBN" on one side.
20 mg	30 count bottle 100 count bottle [redacted]	0088-2161-30 0088-2161-47 [redacted]	Light yellow, triangular film-coated tablet embossed with "ZBO" on one side.
100 mg	3 count blister pack	0088-2162-03	White, round film-coated tablet embossed with "ZBP" on one side.

Store at 25° C (77° F); excursions permitted to 15 - 30° C (59 - 86° F) [see USP Controlled Room Temperature]. Protect from light.

Rx only.

Prescribing information as of September 1998

Manufactured by Usiphar, 60200 Compiegne, France for

Hoechst Marion Roussel, Inc.

Kansas City, MO 64137

Made in France