CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-905 / S-006
20-905 / S-007

Trade Name: **Arava**

Generic Name: **leflunomide**

Sponsor: **Aventis Pharmaceuticals**

Approval Date: **June 13, 2003**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-905 / S-006
20-905 / S-007

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-905 / S-006
20-905 / S-007

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-905/S-006
NDA 20-905/S-007

Aventis Pharmaceuticals
Attention: Joseph Scheeren, PharmD
US Regulatory Liaison
200 Crossing Blvd.
Mail Code BX2-209G
Bridgewater, NJ 08807

Dear Dr. Scheeren:

Please refer to your supplemental new drug applications (NDAs) dated September 4, 2001, received September 5, 2001 (S-006), and dated December 13, 2002, received December 13, 2002 (S-007), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arava™ (leflunomide) tablets, 10 mg, 20 mg and 100 mg.

We acknowledge receipt of your submissions as follows:

Supplement No.	Letter Date	Date Received
S-006	December 13, 2002 (four)	December 13, 2002 (four)
S-006	December 13, 2002	December 16, 2002
S-006	December 26, 2002	December 27, 2002
S-006	December 27, 2002	December 30, 2002
S-006	December 30, 2002	December 31, 2002
S-006	December 31, 2002	January 2, 2003
S-006	April 22, 2003	April 23, 2003
S-006	May 13, 2003	May 13, 2003
S-006	June 9, 2003	June 10, 2003
S-007	September 4, 2001	September 5, 2001
S-007	December 27, 2002	December 30, 2002
S-007	June 9, 2003	June 9, 2003

These supplemental new drug applications provide for the use of Arava™ (leflunomide) tablets, for rheumatoid arthritis. Specifically, the supplemental NDA S-006 provides for revised labeling to support the addition of a claim for improved physical function. The supplemental NDA S-007 provides for revised labeling that includes hepatotoxicity and the potential for death as adverse events.

We have completed our review of these applications, as amended. These supplemental new drug applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text (enclosed).

The final printed labeling (FPL) must be identical to the labeling (package insert) submitted for supplemental NDAs 20-905/S-006 and S-007 on June 9, 2003.

Please submit the FPL electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – NDA." Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-905/S-006, S-007." Approval of these submissions by FDA is not required before the labeling is used.

Effective as of this letter date, we request that you submit the following information for Arava (leflunomide):

1. All reports (US and foreign) of hepatic adverse events regardless of outcome as 15-day Alert Reports.

2. Comprehensive follow-up of all reported cases associated with hepatic adverse events listed in #1 above. The information should be obtained using the active query concept (defined below), as stated in the proposed rule on Safety Reporting Requirements for Human Drug and Biological Products (published in the Federal Register of March 14, 2003 (68 FR 12406)), as a principal of obtaining all possible clinical details in both initial and follow-up reports. This information could be obtained from medical records, laboratory results, supporting documents, hospital discharge summaries, and /or other sources that would sufficiently clarify relevant details of patient treatment, differential diagnosis and the course of clinical events, including complications of liver injury.

3. Active query is defined as direct verbal contact (i.e., in person or by telephone or other interactive means such as a videoconference) by a qualified health care professional representing Aventis, with the initial reporter of a hepatic adverse drug experience. . Active query entails, at a minimum, a focused line of questioning designed to capture clinically relevant information associated with Arava (leflunomide) and the hepatic adverse drug experience, including, but not limited to, information such as baseline data, patient history, physical exam, diagnostic results, and supportive lab results.

4. Quarterly summaries of hepatic events (see above).

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Ms. Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Lee S. Simon, MD
Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lee Simon
6/13/03 11:10:28 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-905 / S-006
20-905 / S-007

LABELING

Rev. XXX

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

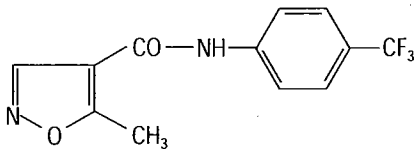
Rx only

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.

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, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, povidone, starch, talc, titanium dioxide, and yellow ferric oxide (20 mg tablet only).

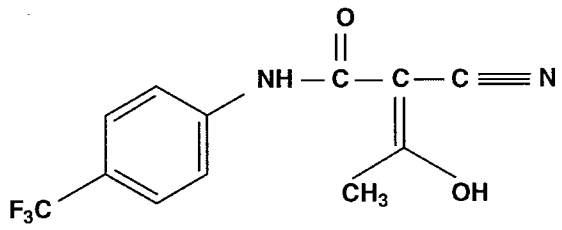
CLINICAL PHARMACOLOGY

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.



A77 1726 (M1)

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 Weeks to Patients (n=54) 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
$t_{1/2}$(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 31 mL/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 PRECAUTIONS - General - Need for Drug Elimination). 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 has 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 phenytoin, tolbutamide, warfarin and many NSAIDs. M1 has been shown to inhibit the formation of 4′-hydroxydiclofenac from diclofenac *in vitro*. The clinical significance of these findings with regard to phenytoin and tolbutamide is unknown, however, there was extensive concomitant use of NSAIDs in the clinical studies and no differential effect was observed. (see PRECAUTIONS – Drug Interactions).

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 showing reduction in signs and symptoms, and inhibition of structural damage. In two placebo controlled trials, efficacy was demonstrated for improvement in physical function.

1. Reduction of signs and symptoms

Relief of signs and symptoms was assessed using the American College of Rheumatology (ACR)20 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, functional ability measure [Modified Health Assessment Questionnaire (MHAQ)], 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.

2. Inhibition of structural damage

Inhibition 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, pp. 233-241), a composite score of X-ray erosions and joint space narrowing in hands/wrists and forefeet.

3. Improvement in physical function

Improvement in physical function was assessed using the Health Assessment Questionnaire (HAQ) and the Medical Outcomes Survey Short Form (SF-36).

In all Arava monotherapy studies, an initial loading dose of 100 mg per day for three days only was used followed by 20 mg per day thereafter.

US301

Study US301, a 2 year study, randomized 482 patients 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 1 mg BID. Primary analysis was at 52 weeks with blinded treatment to 104 weeks.
Overall, 235 of the 508 randomized treated patients (482 in primary data analysis and an additional 26 patients), continued into a second 12 months of double-blind treatment (98 leflunomide, 101 methotrexate, 36 placebo). Leflunomide dose continued at 20 mg/day and the methotrexate dose could be increased to a maximum of 20 mg/week. In total 190 patients (83 leflunomide, 80 methotrexate, 27 placebo) completed 2 years of double-blind treatment.

The rate and reason for withdrawal is summarized in table 2.

Table 2: Withdrawals in US301

	n(%) patients		
	Leflunomide 190	Placebo 128	Methotrexate 190
Withdrawals in Year-1			
Lack of efficacy	33 (17.4)	70 (54.7)	50 (26.3)
Safety	44 (23.2)	12 (9.4)	22 (11.6)
Other[1]	15 (7.9)	10 (7.8)	17 (9.0)
Total	92 (48.4)	92 (71.9)	89 (46.8)
Patients entering Year 2	98	36	101
Withdrawals in Year-2			
Lack of efficacy	4 (4.1)	1 (2.8)	4 (4.0)
Safety	8 (8.2)	0 (0.0)	10 (9.9)
Other[1]	3 (3.1)	8 (22.2)	7 (6.9)
Total	15 (15.3)	9 (25.0)	21 (20.8)

[1] Includes: lost to follow up, protocol violation, noncompliance, voluntary withdrawal, investigator discretion.

MN301/303/305

Study MN301 randomized 358 patients 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. An extension of the study was an optional 6-month blinded continuation of MN301 without the placebo arm, resulting in a 12-month comparison of leflunomide and sulfasalazine (study MN303).

Of the 168 patients who completed 12 months of treatment in MN301 and MN303, 146 patients (87%) entered a 1-year extension study of double blind active treatment (MN305; 60 leflunomide, 60 sulfasalazine, 26 placebo/ sulfasalazine). Patients continued on the same daily dosage of leflunomide or sulfasalazine that they had been taking at the completion of MN301/303. A total of 121 patients (53 leflunomide, 47 sulfasalazine, 21 placebo/sulfasalazine) completed the 2 years of double-blind treatment.

Patient withdrawal data in MN301/303/305 is summarized in table 3.

Table 3: Withdrawals in study MN301/303/305

	n(%) patients		
	Leflunomide 133	Placebo 92	Sulfasalazine 133
Withdrawals in MN301 (Mo 0-6)			
Lack of efficacy	10 (7.5)	29 (31.5)	14 (10.5)
Safety	19 (14.3)	6 (6.5)	25 (18.8)
Other[1]	8 (6.0)	6 (6.5)	11 (8.3)
Total	37 (27.8)	41 (44.6)	50 (37.6)
Patients entering MN303	80		76
Withdrawals in MN303 (Mo 7-12)			
Lack of efficacy	4 (5.0)		2 (2.6)
Safety	2 (2.5)		5 (6.6)
Other[1]	3 (3.8)		1 (1.3)
Total	9 (11.3)		8 (10.5)
Patients entering MN305	60		60
Withdrawals in MN305 (Mo 13-24)			
Lack of efficacy	0 (0.0)		3 (5.0)
Safety	6 (10.0)		8 (13.3)
Other[1]	1 (1.7)		2 (3.3)
Total	7 (11.7)		13 (21.7)

[1] Includes: lost to follow up, protocol violation, noncompliance, voluntary withdrawal, investigator discretion.

MN302/304

Study MN302 randomized 999 patients 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.

Of the 736 patients who completed 52 weeks of treatment in study MN302, 612 (83%) entered the double-blind, 1-year extension study MN304 (292 leflunomide, 320 methotrexate). Patients continued on the same daily dosage of leflunomide or methotrexate that they had been taking at the completion of MN302. There were 533 patients (256 leflunomide, 277 methotrexate) who completed 2 years of double-blind treatment.

Patient withdrawal data in MN302/304 is summarized in table 4.

Table 4: Withdrawals in MN302/304

	n(%) patients	
	Leflunomide 501	Methotrexate 498
Withdrawals in MN302 (Year-1)		
Lack of efficacy	37 (7.4)	15 (3.0)
Safety	98 (19.6)	79 (15.9)
Other[1]	17 (3.4)	17 (3.4)
Total	152 (30.3)	111 (22.3)
Patients entering MN304	292	320
Withdrawals in MN304 (Year-2)		
Lack of efficacy	13 (4.5)	9 (2.8)
Safety	11 (3.8)	22 (6.9)
Other[1]	12 (4.1)	12 (3.8)
Total	36 (12.3)	43 (13.4)

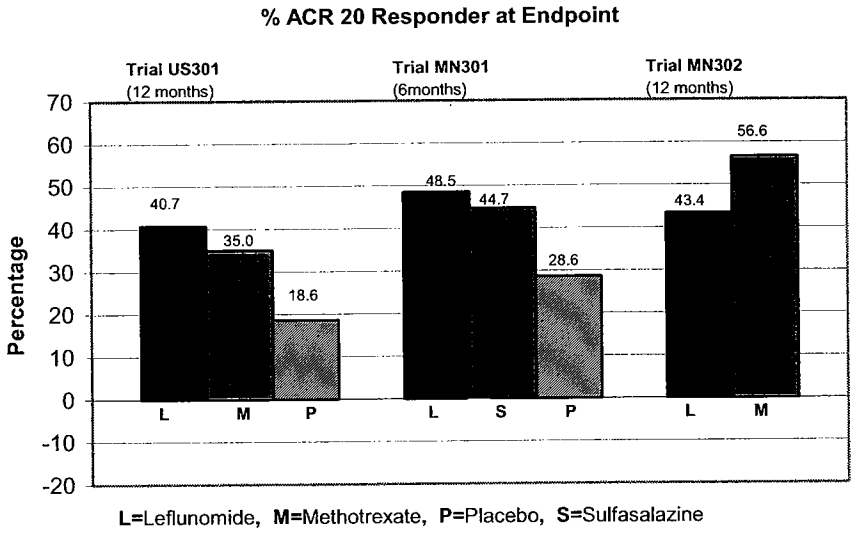
[1] Includes: lost to follow up, protocol violation, noncompliance, voluntary withdrawal, investigator discretion.

Clinical Trial Data

1. Signs and symptoms Rheumatoid Arthritis

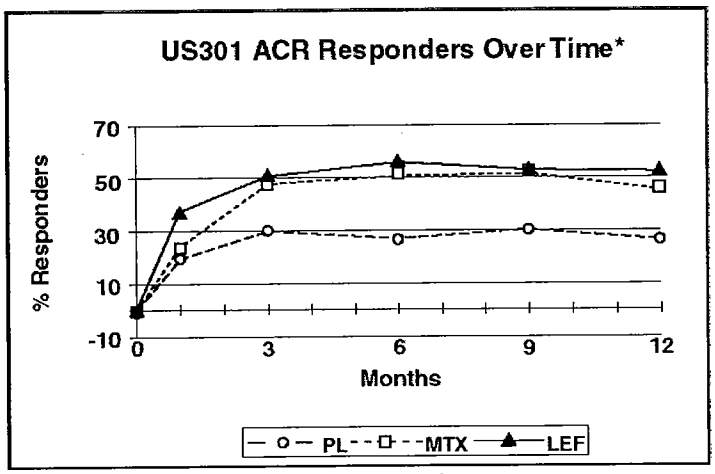
The ACR20 Responder at Endpoint rates are shown in Figure 1. ARAVA was statistically significantly superior to placebo in reducing the signs and symptoms of RA by the primary efficacy analysis, ACR20 Responder at Endpoint, in study US301 (at the primary 12 months endpoint) and MN301 (at 6 month endpoint). 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



	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.

ACR50 and ACR70 Responders are defined in an analogous manner to the ACR20 Responder, but use improvements of 50% or 70%, respectively (Table 5). Mean change for the individual components of the ACR Responder Index are shown in Table 6.

Table 5. Summary of ACR Response Rates*

Study and Treatment Group	ACR20	ACR50	ACR70
Placebo-Controlled Studies			
US301 (12 months)			
Leflunomide (n=178)†	52.2‡	34.3‡	20.2‡
Placebo (n=118)†	26.3	7.6	4.2
Methotrexate (n=180)†	45.6	22.8	9.4
MN301(6 months)			
Leflunomide (n=130)†	54.6‡	33.1‡	10.0§
Placebo (n=91)†	28.6	14.3	2.2
Sulfasalazine (n=132)†	56.8	30.3	7.6
Non-Placebo Active-Controlled Studies			
MN302 (12 months)			
Leflunomide (n=495)†	51.1	31.1	9.9
Methotrexate (n=489)†	65.2	43.8	16.4

* Intent to treat (ITT) analysis using last observation carried forward (LOCF) technique for patients who discontinued early.
† N is the number of ITT patients for whom adequate data were available to calculate the indicated rates.
‡ $p<0.001$ leflunomide vs placebo
§ $p<0.02$ leflunomide vs placebo

Table 6 shows the results of the components of the ACR response criteria for US301, MN301, and MN302. ARAVA was significantly superior to placebo in all components of the ACR response criteria in study US301 and MN301. In addition Arava was significantly superior to placebo in improving morning stiffness, a measure of RA disease activity, not included in the ACR Response criteria. No consistent differences were demonstrated between ARAVA and the active comparators.

Table 6. Mean Change in the Components of the ACR Responder Index*

Components	Placebo-Controlled Studies						Non-placebo Controlled Study	
	US301 (12 months)			MN301 Non-US (6 months)			MN302 Non-US (12 months)	
	Leflu-nomide	Metho-trexate	Placebo	Leflu-nomide	Sulfa-salazine	Placebo	Leflu-nomide	Metho-trexate
Tender joint count[1]	-7.7	-6.6	-3.0	-9.7	-8.1	-4.3	-8.3	-9.7
Swollen joint count[1]	-5.7	-5.4	-2.9	-7.2	-6.2	-3.4	-6.8	-9.0
Patient global assessment[2]	-2.1	-1.5	0.1	-2.8	-2.6	-0.9	-2.3	-3.0
Physician global assessment[2]	-2.8	-2.4	-1.0	-2.7	-2.5	-0.8	-2.3	-3.1
Physical function/disability (MHAQ/HAQ)	-0.29	-0.15	0.07	-0.50	-0.29	-0.04	-0.37	-0.44
Pain intensity[2]	-2.2	-1.7	-0.5	-2.7	-2.0	-0.9	-2.1	-2.9
Erythrocyte Sedimentation rate	-6.26	-6.48	2.56	-7.48	-16.56	3.44	-10.12	-22.18
C-reactive protein	-0.62	-0.50	0.47	-2.26	-1.19	0.16	-1.86	-2.45
Not included in the ACR Responder Index								
Morning Stiffness (min)	-101.4	-88.7	14.7	-93.0	-42.4	-6.8	-63.7	-86.6

* Last Observation Carried Forward; Negative Change Indicates Improvement
1 Based on 28 joint count
2 Visual Analog Scale - 0=Best; 10=Worst

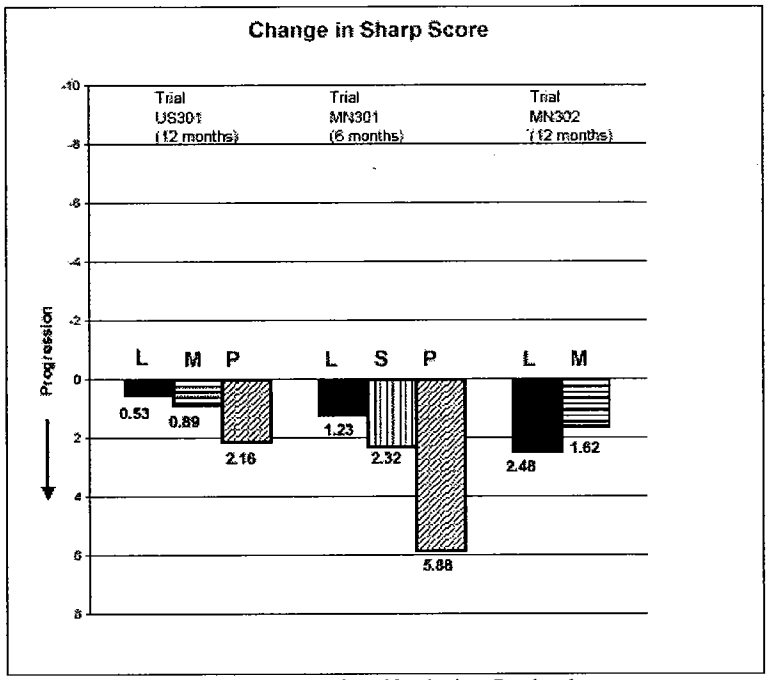
Maintenance of effect
After completing 12 months of treatment, patients continuing on study treatment were evaluated for an additional 12 months of double-blind treatment (total treatment period of 2 years) in studies US301, MN305, and MN304. ACR Responder rates at 12 months were maintained over 2 years in most patients continuing a second year of treatment.

Improvement from baseline in the individual components of the ACR responder criteria was also sustained in most patients during the second year of Arava treatment in all three trials.

2. Inhibition of structural damage

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 inhibiting the progression of disease by the Sharp Score. No consistent differences were demonstrated between leflunomide and methotrexate or between leflunomide and sulfasalazine.

Figure 3



L= Leflunomide; **M**=methotrexate; **S**=sulfasalazine; **P**=placebo

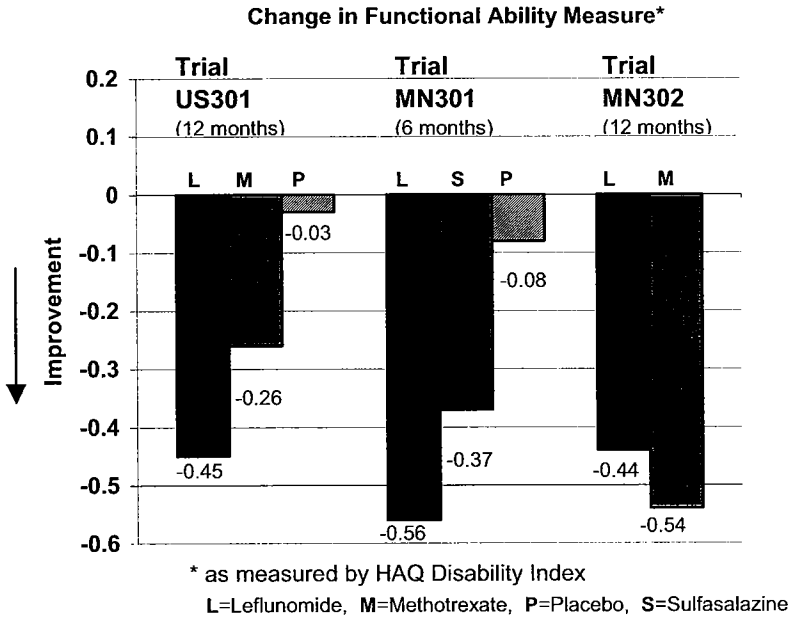
	Comparisons	95% Confidence Interval	p Value
US301	Leflunomide vs. Placebo	(-4.0, -1.1)	0.0007
	Methotrexate vs. Placebo	(-2.6, -0.2)	0.0196
	Leflunomide vs. Methotrexate	(-2.3, 0.0)	0.0499
MN301	Leflunomide vs. Placebo	(-6.2, -1.8)	0.0004
	Sulfasalazine vs. Placebo	(-6.9, -0.2)	0.0484
	Leflunomide vs. Sulfasalazine	(-3.3, 1.2)	NS
MN302	Leflunomide vs. Methotrexate	(-2.2, 7.4)	NS

3. Improvement in physical function

The Health Assessment Questionnaire (HAQ) assesses a patient's physical function and degree of disability. The mean change from baseline in functional ability as measured by the HAQ Disability Index (HAQ DI) in the 6 and 12 month placebo and active controlled trials is shown in Figure 4. ARAVA was statistically significantly superior to placebo in improving physical function. Superiority to placebo was demonstrated consistently across all eight HAQ DI subscales (dressing, arising, eating, walking, hygiene, reach, grip and activities) in both placebo controlled studies.

The Medical Outcomes Survey Short Form 36 (SF-36), a generic health-related quality of life questionnaire, further addresses physical function. In US301, at 12 months, ARAVA provided statistically significant improvements compared to placebo in the Physical Component Summary (PCS) Score.

Figure 4



	Comparison	95% Confidence Interval	p Value
US301	Leflunomide vs. Placebo	(-0.58, -0.29)	0.0001
	Leflunomide vs. Methotrexate	(-0.34, -0.07)	0.0026
MN301	Leflunomide vs. Placebo	(-0.67, -0.36)	<0.0001
	Leflunomide vs. Sulfasalazine	(-0.33, -0.03)	0.0163
MN302	Leflunomide vs. Methotrexate	(0.01, 0.16)	0.0221

Maintenance of effect
The improvement in physical function demonstrated at 6 and 12 months was maintained over two years. In those patients continuing therapy for a second year, this improvement in physical function as measured by HAQ and SF-36 (PCS) was maintained.

INDICATIONS AND USAGE

ARAVA is indicated in adults for the treatment of active rheumatoid arthritis (RA):

1. to reduce signs and symptoms
2. to inhibit structural damage as evidenced by X-ray erosions and joint space narrowing
3. to improve physical function.

(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 (see WARNINGS - Immunosuppression Potential/Bone Marrow Suppression).

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

Immunosuppression Potential/Bone Marrow Suppression

ARAVA is not recommended for patients with severe immunodeficiency, bone marrow dysplasia, or severe, uncontrolled infections. In the event that a serious infection occurs, it may be necessary to interrupt therapy with ARAVA and administer cholestyramine or charcoal (see PRECAUTIONS – General – Need for Drug Elimination). Medications like leflunomide that have immunosuppression potential may cause patients to be more susceptible to infections, including opportunistic infections. Rarely, severe infections including sepsis, which may be fatal, have been reported in patients receiving ARAVA. Most of the reports were confounded by concomitant immunosuppressant therapy and/or comorbid illness which, in addition to rheumatoid disease, may predispose patients to infection.

There have been rare reports of pancytopenia , agranulocytosis and thrombocytopenia in patients receiving ARAVA alone. These events have been reported most frequently in patients who received concomitant treatment with methotrexate or other immunosuppressive agents, or who had recently discontinued these therapies; in some cases, patients had a prior history of a significant hematologic abnormality.

Patients taking ARAVA should have platelet, white blood cell count and hemoglobin or hematocrit monitored at baseline and monthly for six months following initiation of therapy and every 6- to 8 weeks thereafter. If used with concomitant methotrexate and/or other potential immunosuppressive agents, chronic monitoring should be monthly. If evidence of bone marrow suppression occurs in a patient taking ARAVA, treatment with ARAVA should be stopped, and cholestyramine or charcoal should be used to reduce the plasma concentration of leflunomide active metabolite (see PRECAUTIONS – General – Need for Drug Elimination).

In any situation in which the decision is made to switch from ARAVA to another anti-rheumatic agent with a known potential for hematologic suppression, it would be prudent to monitor for hematologic toxicity, because there will be overlap of systemic exposure to both compounds. ARAVA washout with cholestyramine or charcoal may decrease this risk, but also may induce disease worsening if the patient had been responding to ARAVA treatment.

Hepatotoxicity

RARE CASES OF SEVERE LIVER INJURY, INCLUDING CASES WITH FATAL OUTCOME, HAVE BEEN REPORTED DURING TREATMENT WITH LEFLUNOMIDE. MOST CASES OF SEVERE LIVER INJURY OCCUR WITHIN 6 MONTHS OF THERAPY AND IN A SETTING OF MULTIPLE RISK FACTORS FOR HEPATOTOXICITY (liver disease, other hepatotoxins). (See PRECAUTIONS).

At minimum, ALT (SGPT) must be performed at baseline and monitored initially at monthly intervals during the first six months then, if stable, every 6 to 8 weeks thereafter. In addition, if ARAVA and methotrexate are given concomitantly, ACR guidelines for monitoring methotrexate liver toxicity must be followed with ALT, AST, and serum albumin testing monthly.
Guidelines for dose adjustment or discontinuation based on the severity and persistence of ALT elevation are recommended as follows: For confirmed ALT elevations between 2- and 3-fold ULN, dose reduction to 10 mg/day may allow continued administration of ARAVA under close monitoring. If elevations between 2- and 3-fold ULN persist despite dose reduction or if ALT elevations of >3-fold ULN are present, ARAVA should be discontinued and cholestyramine or charcoal should be administered (see PRECAUTIONS - General - Need for Drug Elimination) with close monitoring, including retreatment with cholestyramine or charcoal as indicated.

In clinical trials, ARAVA treatment as monotherapy or in combination with methotrexate 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. Table 7 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 7. Liver Enzyme Elevations >3-fold Upper Limits of Normal (ULN)

	US301			MN301			MN302*	
	LEF	PL	MTX	LEF	PL	SSZ	LEF	MTX
ALT (SGPT)								
>3-fold ULN	8	3	5	2	1	2	13	83
(n %)	(4.4)	(2.5)	(2.7)	(1.5)	(1.1)	(1.5)	(2.6)	(16.7)
Reversed to ≤ 2-fold 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

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

In a 6 month study of 263 patients with persistent active rheumatoid arthritis despite methotrexate therapy, and with normal LFTs, leflunomide was added to a group of 133 patients starting at 10 mg per day and increased to 20 mg as needed. An increase in ALT greater than or equal to three times the ULN was observed in 3.8% of patients compared to 0.8% in 130 patients continued on methotrexate with placebo added.

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 evidence of infection with hepatitis B or C viruses. (See WARNINGS – Hepatotoxicity).

Skin Reactions

Rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients receiving ARAVA. If a patient taking ARAVA develops any of these conditions, ARAVA therapy should be stopped, and a drug elimination procedure is recommended (see PRECAUTIONS - General - Need for Drug Elimination).

Malignancy

The risk of malignancy, particularly lymphoproliferative disorders, is increased with the use of some immunosuppression medications. There is a potential for immunosuppression 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 0.02 mg/L (0.02 μg/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 0.02 mg/L (0.02 μg/mL) by two separate tests at least 14 days apart. If plasma levels are higher than 0.02 mg/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 0.02 mg/L due to individual variation in drug clearance.

PRECAUTIONS

General

Need for Drug Elimination

The active metabolite of leflunomide is eliminated slowly from the plasma. In instances of any serious toxicity from ARAVA, including hypersensitivity, use of a drug elimination procedure as described in this section is highly recommended to reduce the drug concentration more rapidly after stopping ARAVA therapy. If hypersensitivity is the suspected clinical mechanism, more prolonged cholestyramine or charcoal administration may be necessary to achieve rapid and sufficient clearance. The duration may be modified based on the clinical status of the patient.

Cholestyramine given orally at a dose of 8 g 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 to 65% in 48 hours.

Administration of activated charcoal (powder made into a suspension) orally or via nasogastric tube (50 g 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.

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.

Vaccinations

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 (as described in WARNINGS – Use In Women of Childbearing Potential – Drug Elimination Procedure).

Patients should be advised of the possibility of rare, serious skin reactions. Patients should be instructed to inform their physicians promptly if they develop a skin rash or mucous membrane lesions.

Patients should be advised of the potential hepatotoxic effects of ARAVA and of the need for monitoring liver enzymes.

Patients should be instructed to notify their physicians if they develop symptoms such as unusual tiredness, abdominal pain or jaundice.

Patients should be advised that they may develop a lowering of their blood counts and should have frequent hematologic monitoring. This is particularly important for patients who are receiving other immunosuppressive therapy concurrently with ARAVA, who have recently discontinued such therapy before starting treatment with ARAVA, or who have had a history of a significant hematologic abnormality. Patients should be instructed to notify their physicians promptly if they notice symptoms of pancytopenia (such as easy bruising or bleeding, recurrent infections, fever, paleness or unusual tiredness).

Laboratory Tests

Hematologic Monitoring

At minimum, patients taking ARAVA should have platelet, white blood cell count and hemoglobin or hematocrit monitored at baseline and monthly for six months following initiation of therapy and every 6 to 8 weeks thereafter.

Bone Marrow Suppression Monitoring
If used concomitantly with immunosuppressants such as methotrexate, chronic monitoring should be monthly. (see WARNINGS - Immunosuppression Potential/Bone Marrow Suppression).

Liver Enzyme Monitoring
ALT (SGPT) must be performed at baseline and monitored at monthly intervals during the first six months then, if stable, every 6 to 8 weeks thereafter. In addition, if ARAVA and methotrexate are given concomitantly, ACR guidelines for monitoring methotrexate liver toxicity must be followed with ALT, AST, and serum albumin testing every month. (See WARNINGS – Hepatotoxicity.)
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 (TFMA), 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. Pregnancy Registry: To monitor fetal outcomes of pregnant women exposed to leflunomide, health care providers are encouraged to register such patients by calling 1-877-311-8972.

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 PRECAUTIONS – General – Need for Drug Elimination).

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.

Warfarin

Increased INR (International Normalized Ratio) when ARAVA and warfarin were co-administered has been rarely reported.

Pediatric Use

The safety and efficacy of ARAVA in the pediatric population have 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 at one year, the following adverse events were reported, regardless of causality. (See Table 8.)

Table 8. Percentage Of Patients With Adverse Events ≥3% In Any Leflunomide Treated Group

	All RA Studies	Placebo-Controlled Trials				Active-Controlled Trials	
		MN 301/3 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)
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, upper respiratory	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[2]	10%	9%	4%	4%	3%	10%	4%
-New onset of hypertension		1%	<1%	0%	2%	2%	<1%
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[3]	4%	2%	1%	2%	0%	2%	2%
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%

Table 8. Percentage Of Patients With Adverse Events ≥3% In Any Leflunomide Treated Group							
	All RA Studies	Placebo-Controlled Trials				Active-Controlled Trials	
		MN 301/3 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)
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%
Pruritus	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; none in MN301 received folate.

1 Includes all controlled and uncontrolled trials with leflunomide (duration up to 12 months).

2 Hypertension as a preexisting condition was overrepresented in all leflunomide treatment groups in phase III trials.

3 In a meta-analysis of all phase II and III studies, during the first 6 months in patients receiving leflunomide, 10% lost 10-19 lbs (24 cases per 100 patient years) and 2% lost at least 20 lbs (4 cases/100 patient years). Of patients receiving leflunomide, 4% lost 10% of their baseline weight during the first 6 months of treatment.

Adverse events during a second year of treatment with leflunomide in clinical trials were consistent with those observed during the first year of treatment and occurred at a similar or lower incidence.

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, varicose vein, vasculitis, vasodilatation;

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, hyperglycemia, hyperlipidemia, peripheral edema;

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

Nervous System: anxiety, depression, dry mouth, insomnia, neuralgia, neuritis, sleep disorder, sweating increased, vertigo;
Respiratory System: asthma, dyspnea, epistaxis, lung disorder;
Skin and Appendages: acne, contact dermatitis, fungal dermatitis, hair discoloration, hematoma, herpes simplex, herpes zoster, maculopapular rash, nail disorder, skin discoloration, skin disorder, skin nodule, subcutaneous nodule, ulcer skin;
Special Senses: blurred vision, cataract, conjunctivitis, eye disorder, taste perversion;
Urogenital System: albuminuria, cystitis, dysuria, hematuria, menstrual disorder, prostate disorder, urinary frequency, vaginal moniliasis.

Other less common adverse events seen in clinical trials include: 1 case of anaphylactic reaction occurred in Phase 2 following rechallenge of drug after withdrawal due to rash (rare); urticaria; eosinophilia; transient thrombocytopenia (rare); and leukopenia <2000 WBC/mm^3 (rare).

Adverse events during a second year of treatment with leflunomide in clinical trials were consistent with those observed during the first year of treatment and occurred at a similar or lower incidence.

In post-marketing experience, the following have been reported rarely:
Body as a whole: opportunistic infections, severe infections including sepsis that may be fatal;
Gastrointestinal: pancreatitis;
Hematologic: agranulocytosis, leukopenia, neutropenia, pancytopenia, thrombocytopenia;
Hypersensitivity: angioedema;
Hepatic: hepatitis, jaundice/cholestasis, severe liver injury such as hepatic failure and acute hepatic necrosis that may be fatal;
Respiratory: interstitial lung disease;
Nervous system: peripheral neuropathy
Skin and Appendages: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

DRUG ABUSE AND DEPENDENCE

ARAVA has no known potential for abuse or dependence.

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).
There have been reports of chronic overdose in patients taking ARAVA at daily dose up to five times the recommended daily dose and reports of acute overdose in adults or children. There were no adverse events reported in the majority of case reports of overdose. Adverse events were consistent with the safety profile for ARAVA (see ADVERSE REACTIONS). The most frequent adverse events observed were diarrhea, abdominal pain, leukopenia, anemia and elevated liver function tests.
In the event of a significant overdose or toxicity, cholestyramine or charcoal administration is recommended to accelerate elimination (see PRECAUTIONS – General – Need for Drug Elimination).
Studies with both hemodialysis and CAPD (chronic ambulatory peritoneal dialysis) indicate that M1, the primary metabolite of leflunomide, is not dialyzable. (see CLINICAL PHARMACOLOGY – Elimination).

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.

Elimination of the loading dose regimen may decrease the risk of adverse events. This could be especially important for patients at increased risk of hematologic or hepatic toxicity, such as those receiving concomitant treatment with methotrexate or other immunosuppressive agents or on such medications in the recent past. (see WARNINGS – Hepatotoxicity)

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 must 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	0088-2160-30 0088-2160-47	White, round film-coated tablet embossed with "ZBN" on one side.
20 mg	30 count bottle 100 count bottle	0088-2161-30 0088-2161-47	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.

Rev. xxxx

Manufactured by
Usiphar, 60200 Compiegne, France
for
Aventis Pharmaceuticals Inc.
Kansas City, MO 64137

Made in France

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-905 / S-006
20-905 / S-007

MEDICAL REVIEW

Team Leader and Deputy Division Director's Secondary Review
NDA 20905 Supplement 06

Submission date: December 12, 2002
Review date: June 5, 2003
Primary Reviewer: Tatiana Oussova MD

The marketing approval for leflunomide in 1998 was based on placebo and active controlled studies of leflunomide which demonstrated efficacy of leflunomide for the signs and symptoms of rheumatoid arthritis (RA). The primary endpoint in these studies was the ACR 20 response rate at 6 or 12 months. An additional endpoint of study included improvement in the Health Assessment Questionnaire (HAQ) score. The "disability index" section of this instrument provides information on physical function as described in the Medical Officer's review by Dr. Oussova. As discussed in that review, the current Guidance for Industry (dated 1999) for the development of products for the treatment of RA includes an [redacted] ccording to the [redacted] The instruments described in the Guidance document include the HAQ and the Arthritis Impact Measure Scales (AIMS). Several issues have become apparent since the issuance of this guidance.

1. The term disability has evolved since the 1999 guidance was published. At the time of publication the terms physical function and disability were not frequently distinguished. Since that time the concept of disability has been refined and is no longer synonymous with impaired physical function. Functional impairment or limitation of physical function is currently defined as a restriction or lack of ability to perform basic generic actions in daily life such as lifting, bending, walking or eating. Disability reflects difficulty, limitation or inability to perform activities expected of a person within a social and physical environment. This distinction is well outlined in a recent publication by Escalante and Del Rincon (1). The International Classification of Functioning, Disability and Handicap was ratified by the 54th World Health Organization World Health Assembly in 2001. This document provides the generic framework for the RA specific discussion in the Escalante and Del Rincon article. In addition, the term disability has legal implications and definitions related to worker's compensation and social security. Thus for the purposes of describing benefits of medical therapy using instruments such as the HAQ that assess changes in physical function (resulting from clinical impairments such as pain and tender/swollen joints) "improvement in physical function" [redacted] Physical function is a domain that is associated with improvement in signs and symptoms and thus may be responsive within a period of weeks to months rather than years

and may be most appropriately assessed in the time frame currently used to assess therapies for RA (6 months).

2. Long term placebo controlled clinical study of therapies for highly symptomatic conditions such as RA are increasingly difficult to conduct. Based on ethical concerns related to long term placebo controlled study; in the current NDA supplement, the sponsor incorporated a mandatory change in therapy at 16 weeks in the pivotal study of 12 months duration (US301) for subjects with less than an ACR 20 response. While alternatives to placebo controlled study exist, statistical analysis of studies with high withdrawal rates or changes in therapy is complex as described in the statisticians review of the current NDA supplement by Dr. Suktai Choi as well as in the consultation report of Dr. Jennifer Anderson appended to the medical officers review. Comparator therapy for noninferiority trials must be approved for the proposed indication and must have a stable and well-established effect size.

The current guidance document does not specify how to deal with such issues.

In the future, consideration should be given to revising the RA guidance document to clarify whether physical function is in fact a reflection of improvement in signs and symptoms rather than a discrete indication. Consideration should be given to whether "[ ]

The database submitted by the sponsor in the current NDA supplement has been extensively reviewed by medical and statistical reviewers. Improvement in physical function as reflected by the HAQ, HAQ DI ("disability index" scale) or MHAQ was demonstrated and shown to be superior to placebo at 6 and 12 months in study US301 and at 6 months in study MN 301. The primary analyses employed a last observation carried forward (LOCF) imputation for missing data. Multiple sensitivity analyses using more conservative imputation techniques (see statisticians review) supported the LOCF analysis when applied to the study with the highest level of missing data, US301. The sponsor has provided adequate evidence to support labeling changes reflecting this improvement in physical function.

1. Escalante A., Del Rincon I. The Disablement Process in Rheumatoid Arthritis, Arthritis and Rheumatism 2002, 47 (3) 333-342

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/s/

Lawrence Goldkind
6/6/03 01:00:32 PM
MEDICAL OFFICER

Lee Simon
6/11/03 06:27:29 PM
MEDICAL OFFICER

Clinical Review Cover Sheet

Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Product (HFD-550)

NDA 20-905/supplement 006

Date of Submission:	**December 13, 2002**
Review Date:	**June 10, 2003**
Drug Name:	**Arava**
Generic Name:	**Leflunomide**
Chemical Name:	**sodium salt of N-{[4-(5-methyl-3-phenylisoxazol 4-yl)phenyl]sulfonyl}propanamide**
Applicant:	**Aventis**
Pharmacologic category:	**DMARD**
Proposed Indication:	**improvement in physical function in patients with rheumatoid arthritis**
Dosage forms and route:	**Tablets, 10 and 20 mg**
Medical reviewer:	**Tatiana Oussova, MD, MPH**
Project Maanger:	**Jane Dean, RN, MSN**

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Clinical Review for NDA 20,905

I. Introduction and Background

A. Review of regulatory history

Rheumatoid arthritis (RA) is well recognized as a serious and progressively debilitating condition. This disease cannot be cured, but disease control can be improved due to availability of effective drugs. Physical disability is a serious manifestation of RA that has a significant effect on patients' everyday life. One of the primary therapeutic goals is to improve and maintain physical functioning of RA patients and therefore to improve their quality of life. From the armamentarium of drugs available to treat patients with RA, only infliximab has an approved indication for improving physical function.

Arava (leflunomide) received marketing approval on 10 September 1998 for the treatment of active RA to reduce signs and symptoms and to retard structural damage as evidenced by X–ray assessment of erosions and joint space narrowing. However, the inclusion in the labeling of claims regarding the [redacted] The FDA guidance for industry on "Clinical development program for drugs, devices, and biological products for the treatment of rheumatoid arthritis (RA)", dated February 1999, recommends a minimum of 2-year data before considering a [redacted] It states:

[redacted]

Based on the guidance, the Sponsor continued the three original NDA studies to obtain blinded (study US301 had also a placebo arm) 24-month data to support the [redacted] indication. After the studies were completed, the Sponsor submitted supplemental NDA

providing accumulated 2-year data from Phase III studies in support of an indication for _____ as evidenced by improved physical function.

On March 22, 2000 the Sponsor submitted a Request for Fast Track Designation and a Request for rolling submission. On May 16, 2000 the FDA designated the NDA supplement 006 for Arava (leflunomide) a Fast-Track for the as evidenced by improved physical function. S-006 was submitted in two steps on June 7, 2000 and August 30, 2000. Amendments to sNDA 20-905/S-006 were submitted on November 17 and 27, 2000; December 4, 7, 11, 22, and 27 (2), 2000; and on January 4, 9, and 23, 2001. The Arthritis Advisory Committee (AC) was scheduled for March 2001 to discuss this claim-related issues but on February 1, 2001, the Sponsor withdrew sNDA 20-905/S-006. The Sponsor re-submitted sNDA 20-905/S-006 in December, 2002.

Public Citizen's Health Research Group (PCHRG) submitted a petition on March 28, 2002 requesting to remove Arava from the market due to its toxicity and lack of increased efficacy compared with methotrexate, the current standard therapy for RA. To address the concerns raised by this Petition, the FDA has conducted extensive and comprehensive safety reviews along with revisiting the indication for improvement in physical function. Both safety and efficacy data for the indication of improvement in physical function were presented to Arthritis AC in March 2003.

Conclusions from AC:

1. There is an acceptable benefit-to-risk profile for leflunomide
2. The data on leflunomide presented by the sponsor is adequately robust to support labeling for improvement in physical function
3. The HAQ seems to remain the gold standard and the most comprehensive validated tool to assess physical function in patients with RA
4. Clinical trials in RA of 6-12 months duration are acceptable for assessing changes in physical function
5. Disability may not be the appropriate term for communicating the clinical benefit reflected by changes in the HAQ as noted by AC Chairman Dr. Firestein: ***" Disability is a complicated word with many connotations that we'd like to avoid and physical function is the word that we'd like to promote".***

Reviewer's comments:

- ***Though the Sponsor submitted data on HAQ, PET, MOS, and SF-36, this review will concentrate on analysis of HAQ data as a primary outcome measure.***
- ***In addition, this reviewer would like to point out that the Guidance document does not specifically require 2 years of placebo-controlled data. Requiring 2-year placebo-controlled data in RA trials is very problematic as will be further discussed in this review. There was a general awareness of the problems associated with the long-term placebo design, but there is no discussion of high rates of placebo dropouts and how to approach this problem in statistical analysis in RA Guidance document.***

B. Physical function vs. disability measures

1. HAQ (see attachment #1)

The **HAQ** is an acronym for health assessment questionnaire. This is a validated instrument developed to assess disease-specific physical function in patients suffering from RA. The HAQ is one component of the ACR response criteria. The HAQ is scored from zero, indicating no impairment, to three, indicating inability to perform activities of daily living independently. An increase of one unit per year over the first two years of disease results in a 90 percent greater disability over the next three years (Fries, 1982).
HAQ assesses 5 dimensions of health outcome:

1. Disability (8 categories of daily activities; **makes up HAQ DI**)
2. Discomfort (HAQ VAS pain scale; Patient Global VAS)
3. Drug side effects (Medical; Toxicity Index; Surgical)
4. Dollar cost (direct and indirect)
5. Death (time to death, cost of death)

The Health Assessment Questionnaire has been evaluated in a variety of clinical trials and settings over the years, particularly for physical function in activities of daily living. It is recognized in the RA guidance document as an adequately validated measure for use as the primary outcome measure in trials of physical function in rheumatoid arthritis.

2. HAQ Disability Index (HAQ DI)

There are 20 questions in 8 categories of functioning that represent a comprehensive set of functioning activities-dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. It uses the scores of the worst item within each of the eight categories, modified by the use of devices and aids. In the event that a patient indicates that he/she uses a device or aid to perform a task, the score for the associated category increases to 2 *("able to do with much difficulty")* if it was previously 0 or 1.

The HAQ DI has been shown to significantly correlate with a wide variety of health status measures, including self-report measures, signs and symptoms of rheumatoid arthritis, assessment of morbidity and mortality (Wolfe, 1998).

3. Medical Outcomes Study 36-Item Short Form (SF-36)

The SF-36 is a generic health-related quality of life instrument in addition to being a disease-specific instrument. It is designed to represent eight of the most important health concepts: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. In addition, a single question assesses reported health transition.

Each domain generates a transformed score in the range 0-100, with 0 being the worst score and 100 the best.
In addition to the scores for the eight SF-36 domains, two summary scores are calculated for the physical and mental component summary scores (PCS and MCS, respectively). The two summary scores are calculated based on combination of the eight SF-36 domains. The instrument was developed so that the general population has a mean score of 50 with a standard deviation of 10.
As per Guidance document: "*Since the full effect of RA on a patient is not captured without the use of more general HR-QOL (health-related quality of life) measures, a validated measure such as SF-36 should also be collected and patients should not worsen on these measures over the duration of the trial.*"

II. Description of Clinical Data and Sources

A. Overview of clinical studies

The approval of Arava was based on 1-year data from the three Phase III pivotal trials that were submitted in the original NDA with ACR20 as a primary endpoint. All three of the trials were multicenter, double-blind, parallel-group studies and extended to 2 years to accumulate necessary efficacy and safety data.
One of these studies, US 301, compared leflunomide with methotrexate and placebo over 2-year period.
A second study, MN305, is the 1-year extension of 2 studies: 6-month placebo-controlled MN301 and its 6-month extension MN303. MN305 compared leflunomide with sulfasalazine in a second year of active treatment (placebo control was only used in initial study MN301 for the first 6 months).
The third study, MN 304, which is the 1-year extension of 1-year MN302, compared leflunomide with methotrexate in the second year of active treatment.
All three studies gathered information on patient physical function for 2 years by measuring HAQ and MHAQ. In addition to that, US301 used health-related quality of life instrument SF-36. Note that the SF-36 was not included in the leflunomide European MN studies, which were designed in 1993 and initiated in 1994, since valid translations were not available for many countries at that time.

US301

The study was designed as a 2 year double-blind trial to provide long-term data on the safety and efficacy of leflunomide compared with placebo and methotrexate in the treatment of patients with active RA. The primary, protocol-defined endpoint for the study was ACR20 response after 12 months of treatment in the initial therapy phase. This primary 12-month analysis for patients treated at the 42 US study sites was previously reported in the original NDA submission (see reviews of NDA 20905 dated 1998). For ethical reasons, the study design provided for mandatory, blinded reassignment of patients insufficiently responsive (protocol-defined) at 16

weeks of study treatment or were withdrawn due to significant toxicity, or persistent laboratory abnormalities. Patients who were initially randomized to methotrexate or placebo in the initial therapy phase received leflunomide in the alternative therapy phase; patients originally randomized to receive leflunomide received methotrexate in alternative therapy phase.
To support a claim for [redacted] improvement in physical function, the full 24-month data of the initial therapy phase as well as results from alternative therapy phase (1-year data) for patients treated at the 42 US and 5 Canadian suites, were submitted.

In support of a claim for [redacted] nd improvement in physical function, the following questionnaires were used in US301 to gather information on patient's physical function and health-related quality of life **at baseline, weeks 24, 52, 104, or when the patient switched medication or left the study.**

- Health Assessment Questionnaire **(HAQ)**
- Problem Elicitation Technique (PET)
- 36-Item Short-Form (SF-36) divided into physical component (SF36-PC) and mental component (SF36-MC)
- Medical Outcome Study (MOS) current health perceptions scale
- Work Productivity Questionnaire (WPO): Items on work problems and work productivity were abstracted from the 1994 National Opinion Research Center Survey.

Modified HAQ **(MHAQ)** was measured during visits at weeks **4, 6, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 58, 64, 70, 76, 82, 88, 94, 100, 104.**

Table 1.
Patient disposition in US301

Patient status	LEF No. (%) subjects	Placebo No. (%)	MTX No. (%)	Total No. (%)
Enrolled (ITT) cohort	190 (100%)	128 (100%)	190 (100%)	508 (100%)
Entered 2nd yr. of treatment	98 (52%)	36 (28%)	101 (53%)	235 (46%)
Completed 24 months of treatment	83 (44%)	27 (21%)	80 (42%)	190 (37%)
Alternate therapy				
Enrolled	25 to MTX	56 to LEF	35 to LEF	116
Completed 1 yr. on new therapy	16 (64%)	34 (60%)	17 (48%)	67 (57%)

Reviewer's comments:

- ***The number of patients remaining at the end of year 2 is small. Out of 190 patients randomized into the trial to receive leflunomide, 83 completed 2 years in the trial, and 58 on leflunomide had 2-year data for HAQ. 80 (42%) patients on methotrexate completed 2 years in the trial, and only 27 (21%) patients on placebo completed 2 years in the trial.***

- ***As noted earlier, there is no discussion of anticipated high rates of dropouts and how to approach this problem in statistical analysis in RA Guidance document. Analysis of data is problematic and several ways of imputing missing data need to be considered.***

- ***Additionally complicating the analysis is that the study protocol required switching patients to alternative therapy at week 16 if there was inadequate response to initial therapy. Substantial numbers of patients were excluded from primary analysis because they were switched to alternative therapy. This results in informative censoring of the patients switched to alternative treatments. Despite the above deficiencies of the trial design, this reviewer thinks this particular group of patients represents a substantial number and should be included into statistical analysis. As per ICH Guidance on Statistical Principles for Clinical trials, " the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance with the planned course of treatment".***

MN 301/303/305

MN305 was a double-blind 52-week extension to the 24-week study **MN303**, which in turn was a double-blind extension to the 24-week study **MN301**. The objectives of the studies MN301/303/305 were to investigate the safety of leflunomide during long-term use in RA patients, to assess the relative efficacy and safety profile of leflunomide compared with sulfasalazine, and to investigate population pharmacokinetics. In the original protocol for **MN305**, blinded treatment was to be continued until the database for **MN301** has been unblinded. The double-blind treatment period was, however, subsequently extended in two amendments to allow patients to complete 2 years of treatment. Patients who received leflunomide or sulfasalazine in **MN301** continued on their respective medication in **MN303** and **MN305**. Patients who received placebo in **MN301** were switched to sulfasalazine in a blinded manner at the start of **MN303** and continued on sulfasalazine in **MN305** (placebo/sulfasalazine group). At the start of **MN305**, all patients continued on the same daily dosage of leflunomide or sulfasalazine that they had been taking at the completion of **MN303**. Results of **MN301** and **MN303** were previously reported in the original NDA submission.

The **HAQ** was used in **MN 301/303/305** to gather information on patients functional impairment for 2 years. Assessments were made **at baseline, Weeks 24, 52, 104, or when the patient discontinued early.**

Table 2
Patient disposition in MN301/303/305

Study/Patient status	LEF No. (%)	Placebo No. (%)	Sulfasalazine No. (%)	Total No. (%)
MN301				
Enrolled (ITT cohort)	133 (100%)	92 (100%)	133 (100%)	358 (100%)
Completed (**6 mo**)	96 (72%)	51 (55%)	83 (62%)	230 (64%)
MN303				
Enrolled*	80 (60%)	41 to SSZ**	76 (57%)	197 (55%)

Completed (**12 mo**)	71 (53%)	29	68 (51%)	168 (47%)
MN305				
Enrolled*	60 (45%)	26	60 (45%)	146 (41%)
Completed	53 (40%)	21	47 (35%)	121 (34%)

* Some patents who completed MN301 or MN303 elected not to continue in the next extension protocol.
** Patients who received placebo in MN301 were switched to sulfasalazine in a blinded manner at the start of MN303 and continued on sulfasalazine in MN305. These patients are not included in the analyses of the sulfasalazine treatment group.

Reviewer's comments:

- ***In the leflunomide arm, 53(40%) out of 133 randomized patients, stayed in the trial for 2 years. 47 (35%) out of 133 initially randomized to sulfasalazine, stayed in the trial for 2 years. Again, the small number of patients remaining in the trial for 2 years created problems with analyzing the data.***

- ***In addition, there are no placebo data beyond 6 months as all placebo patients switched to sulfasalazine at 6 months. 21 patients completed 18 month on sulfasalazine therapy. Those patients were considered droupouts and were not included in analyses.***

- ***This reviewer thinks that those dropouts should not be neglected and alternative methods of analyzing the data that would include the dropouts need to be considered (see Jennifer Anderson statistical review).***

- ***A comparison with the placebo arm at 6 months however may allow for the separation of active treatment from placebo.***

MN302/304

The study was a double-blind extension of study **MN302** to investigate the safety of leflunomide during long-term use in RA patients, to assess the relative efficacy and safety profile of leflunomide compared with methotrexate during long-term treatment, and to investigate population pharmacokinetics. In the original protocol for **MN304**, blinded treatment was to be continued until the database for **MN302** had been unblinded. The double-blind treatment period was, however, subsequently extended by an amendment to allow all patients to complete 2 years of treatment. At the start of **MN304**, all patients continued on the same dosage of leflunomide or methotrexate that they had been taking at the completion of **MN302**. Results of **MN302** were previously reported in the original NDA submission.

The **HAQ** was used in **MN302/304** to gather information on patient functional impairment over 2 years. Assessments were made **at baseline, weeks 24, 52, 104, or when the patient discontinued early.**

Table 3

Patient disposition in MN302/304

Study/Patient status	LEF No. (%)	MTX No. (%)	Total No. (%)
MN302			
Enrolled (ITT cohort)	501 (100%)	498 (100%)	999 (100%)
Completed (12 months)	349 (70%)	387 (78%)	736 (74%)
MN304			
Enrolled*	292 (58%)	320 (64%)	612 (61%)
Completed (24 months)	256 (51%)	277 (56%)	533 (53%)

Some patients who completed MN302 elected not to continue in MN304.

Reviewer's comments:

- ***There is no placebo arm in this study that makes an assessment of efficacy difficult.***

- ***This is the largest trial out of 3 trials. It has less problems with droupouts at the end of 2 years. However, it cannot be a pivotal trial in assessment of efficacy due to lack of placebo arm and lack of superiority to methotrexate, a drug unapproved for improvement in physical function or disability.***

B. Postmarketing Experience

Comprehensive analysis of postmarketing safety has been done by Dr. Lawrence Goldkind (see his review for more details).
Ongoing labeling review will update the label on leflunomide safety profile based on post-marketing surveillance and review of the US and foreign data.

C. Literature Review

Extensive literature review was performed by this reviewer to gather information on physical function and disability associated with RA and on studies performed to assess those outcomes. Reference is also made to reviews of biological DMARDs done by CBER . Based on the literature review, the following conclusions have been reached:

1. Physical function is a claim for an important patient-reported outcome and is distinct from disability
2. HAQ is an appropriate instrument for evaluating physical function in pivotal trials

III. Clinical Review

An analysis of the current data was performed at the time of original submission of SNDA 20-905/S-006 in 2000 by Dr. Kent Johnson, and executive summary of his review is attached (attachment #2).

Given previous analysis and evolution in a field of understanding of physical function and disability, reassessment of disability versus physical function as an indication by AC meeting on 3/4/2003, this review raises the following questions:

1. *What is the nature of physical function /disability -are they the same?*
2. *Are 2 years of controlled data for durability of efficacy and/or safety necessary?*
3. *Are 2- year studies with placebo-control feasible or ethical?*
4. *Can physical function and disability be viewed as separate indications, or as a part of disease signs/symptoms?*

There are several definitions of disability. The Americans with Disabilities Act defines disability as: "*...physical or mental impairment that substantially limits one or more of the major life activities of such individual*".
In 1998, the WHO presented a revision of The International Classification of Impairments, Activities and Participation. By the revised statement, a disease may result in impairment that affects activity and participation, and these three factors may interrelate. Activity is defined as a person's functional level and may be limited in nature, duration, and quality. Participation is involvement in life situations in relation to impairment, activities, health conditions, and it may be restricted in nature, duration, and quality. In this classification, activity limitations equate with disability, and participation restriction equates with handicap. Impairment occurs at body level, activity at the whole person level, and participation at the societal level. In this model, medical treatment is directed toward impairment. In other words, a patient might remain disabled but his or her physical function, or impairment, can improve due to treatment.
Because one of the goals of RA therapy is to improve patient's day-to -day functioning, or limit the degree of functional impairment, it seems logical to separate the claim from the claim improvement in physical function. While disability may be most appropriately documented over several years, physical function may respond in a shorter time interval and can be viewed as reflective or related to improvements in signs and symptoms.

ong-term data would be needed to actually show that

Guidance document.

Placebo-controlled clinical trials are still considered to provide the most convincing basis for assessing the efficacy and safety of drugs. However, placebo-controlled trials (especially long-term trials of at least 2 years' duration) are difficult to conduct in highly symptomatic conditions due to high rate of dropouts in a placebo arm. The dropout rate in active treatment arms is also quite high due to either side effects or failure to achieve an adequate disease control. In addition to that, use of placebo for longer than 6 months in diseases such as RA is of concern due to ethical considerations.

Summary of previous clinical and statistical reviews by Drs. K. Johnson and S. Choi dated 2000 (attachments # 2, 3)

A: Pivotal Analyses:

The analyses of patient-reported outcomes were performed on the intention-to-treat (ITT) and year-2 cohorts in order to evaluate physical function and health-related quality of life.
The ITT cohort included all patients initially enrolled into US301, MN301, and MN302 who took at least one dose of study medication.
The year-2 cohort included all patients initially enrolled into US301, MN301, and MN302 and who entered a 2nd year of treatment.

The following comparisons were performed:

- Leflunomide versus placebo in the ITT population using last-observation-carried-forward (LOCF) methodology at the primary endpoint for each protocol and at 24 months
- Leflunomide versus methotrexate in the ITT population using LOCF at the primary endpoint for each protocol and at 24 months
- Leflunomide versus sulfasalazine in the ITT population using LOCF at the primary endpoint for each protocol and at 24 months
- Leflunomide versus methotrexate in the year-2 cohort using LOCF
- Leflunomide versus Sulfasalaizne in the year-2 cohort using LOCF
- To assess the maintenance of effects during the second year of treatment, the 24-month data were compared with the 12-month data within each treatment group for the year-2 cohort using LOCF.

Reviewer's comments:

- ***ACR20 was a primary protocol-defined outcome measure***

- ***HAQ and SF-36 were not pre-specified as primary outcomes. These represent non-pivotal analyses and P values are nominal.***

Comparison	HAQ	SF-36 PC	ACR20
US301 Lef vs Plc 12 months	-0.460 (-0.622,-0.298) p<0.001	7.844 (4.164,10.523) p<0.001	26.0% (15.2,36.8) p<0.001
24 months	-0.397 (-0.539,-0.255) p<0.001	6.581 (3.725,9.437) p<0.001	31.8% (21.7,41.9) p<0.001
US301 Lef vs. Mtx 12 months	-0.231 (-0.411,-0.050) p=0.0121	2.408 (-1.092,6.908) NS	6.7% (-3.6,17.0) NS
24 months	-0.236 (-0.381,-0.091) p=0.002	3.955 (0.963,6.946) p=0.010	5.2% (-5.0,15.3) NS
US301 Mtx vs Plc 12 months	-0.230 (-0.412,-0.048) p=0.014	5.049 (1.649,8.449) p=0.009	19.3% (8.5,30.1) p<0.001
24 months	-0.164 (-0.305,-0.022) p=0.023	2.729 (-0.122,6.580) NS	26.7% (16.7,36.7) p=0.001
MN301 Lef vs Ssz 12 months	-0.162 (-0.314,-0.010) p=0.037	N/A	0.1% (-12.0,12.1) NS
24 months	-0.175 (-0.330,-0.019) p=0.028	N/A	8.4% (-3.7,20.4) NS
MN302 Lef vs Mtx 12 months	0.087 (0.014,0.160) p=0.019	N/A	-14.1% (-20.2,-8.02) p<0.001
24 months	0.106 (0.028,0.183) p=0.008	N/A	-11.3% (-17.5,-5.2) p<0.001

These analyses use LOCF but excluded all data after patients were switched from initial randomized allocation.

At 12 months, in trial US301 the leflunomide treatment group showed significant improvement from baseline to endpoint compared to placebo in all HAQ scale scores and Physical Component of SF-36 score.

By ITT/LOCF analysis of HAQ/MHAQ data leflunomide was statistically significantly superior to placebo, methotrexate and sulfasalazine in trials US301 and MN301. Leflunomide was statistically significantly inferior to methotrexate in MN302 though improvement occurred in both active treatment groups.
Leflunomide was statistically significantly superior to placebo in US301 by ITT analysis of SF-36 physical function subscale. There was no statistically significant difference between leflunomide and placebo in SF-36 mental function subscale. There was no statistically significant difference between leflunomide and methotrexate by ITT analysis of SF-36 though both active groups showed improvement from the baseline.

Additionally, initial medical review noted the correlation between improvement in physical function and responder status by ACR20 criteria.

Statistical review of the second year data was performed by Dr. Suktae Choi and focused on the analysis of the HAQ, the modified HAQ (MHAQ) and SF-36 measurements.
The endpoint reviewed was the change from baseline at the end of year 2 (see original review by Dr. Suktae Choi for more details). By LOCF analysis leflunomide was statistically significantly superior to placebo, methotrexate and sulfasalazine in the placebo-controlled trials US301 and MN301, but favored methotrexate over leflunomide in MN302/304.
Dr.Choi pointed out that the high rate of dropouts in all groups and early dropouts caused a high rate of missing data. In US301 trial most dropouts occurred at weeks 16, when trial design mandated blinded reassignments of patients insufficiently responsive at four months (protocol-defined) to alternative therapy. Patients who received placebo in MN301 were switched to sulfasalazine in a blinded manner at the start of MN303 and continued on sulfasalazine in MN305. These patients were not included in the analyses of the sulfasalazine treatment group.

Reviewers attempted to analyze the robustness of results that relied on LOCF. This was done by determining how deviant missing patient data could be, compared to patients with data, and still maintain statistical significance (for more details, please, see attached of clinical review by Dr. Kent Johnson). A sensitivity analysis was performed by Dr. Suktae Choi to evaluate the robustness of the analyses described above. Demographics were compared between completers and incompleters, and no differences were detected.

This analysis demonstrated that about one-half of the difference in effect seen between leflunomide and placebo or between leflunomide and methotrexate completers could be lost in the non-completers and the <0.05 inference still hold. In other words, when ITT/LOCF analysis demonstrated highly statistically significant results, placebo dropouts would need to have

substantially better results than placebo completers to invalidate the conclusion of ITT/LOCF analysis.

Despite the reassuring sensitivity analysis, the statistician and medical officer at the time of initial review of NDA 20-905/S-006 had concerns over the adequacy of data given the need for imputation of >50% of data. An Advisory Committee was scheduled to discuss this issue but the sponsor withdrew the application.

Reviewer's comments:

- ***1-year data analysis provides an evidence of efficacy of leflunomide in improving a physical function. However, analysis of 2-year data was hard to interpret due to significant amount of missing data though the amount of missing data in leflunomide arm was comparable to that seen in methotrexate arm in study US301. Data imputation methods that were used at the time of original analysis such as LOCF were not robust enough to make any conclusions.***

- ***MN301/303 provides replicated evidence of efficacy for leflunomide in improving physical function after 1 year of treatment.***

B. Supportive Analyses (see current statistical review by Dr. Suktae Choi, attachment #3)

In this particular database, the most robust data exists for the first 16 weeks (or 4 months) of trial in study US301 before the patients were mandated to switch to alternative therapies. For the pivotal efficacy analysis, this reviewer consider 6 months of trial duration to be appropriate. March 2003 Arthritis Advisory Committee agreed that RA trials of 6-12 months duration would provide sufficient amount of data in support of a claim for improvement in physical function. Statistical reviewer considers LOCF analysis at 6 months appropriate because time-wise it is close to 4 months when the switch to alternative therapy occurred. Statistical analysis (LOCF) of data from studies US301 and MN301 performed by Dr. Suktae Choi showed that leflunomide was statistically significantly superior to placebo at 6 months of treatment as assessed by HAQ, MHAQ, and SF-36. Superiority to placebo was demonstrated consistently across all HAQ subscales in both placebo-controlled studies (US301 and MN301).

Due to the amount of missing data at month 12, sensitivity analysis of LOCF results are appropriate. Sensitivity analyses, as discussed in Dr. Choi's review, using three approaches to replace missing data within a treatment group showed superiority of leflunomide over placebo for HAQ, MHAQ and SF-36 PCS at 12-month time point in study US301.

Reviewer's comments:

- ***Studies submitted with this application, demonstrated that leflunomide significantly improves physical function compared to placebo, in a placebo controlled six month trial, a***

placebo controlled 12 month trial, with further confirmation in a non-placebo controlled 12 month trial showing a consistent degree of improvement.

- ***Mean HAQ scores declined progressively in all 3 trials with LEF treatment.***
- ***In Study US301, which used multiple patient reported outcome measures (the HAQ and the SF-36, in particular) efficacy results were consistent across measures.***

IV. Integrated Review of Safety

See review by Dr. Lawrence Goldkind.

V. Conclusions/Recommendations

- *Comprehensive analyses of data from two pivotal replicate studies (US301 and MN301/303) provide convincing evidence to support the indication that leflunomide improves the physical function at time periods up to 12 months.*
- *The data beyond 12 month period suggest the effect is maintained however the amount of missing data in all treatments arms makes a conclusion somewhat less robust.*
- *All pivotal trials submitted with original NDA and extended to collect data on physical function, used validated measures of physical function such as HAQ, MHAQ, HAQ DI along with validated generic health-related quality of life measure (SF-36).*
- *The metrics that were used to access the physical function such as HAQ, HAQ DI, and SF-36 appear appropriate for this indication and its appropriateness was discussed by the AC meeting in March, 2003.*
- *All three trials demonstrated previous improvement in sign and symptoms, HAQ scores correlated with clinical response (measured by ACR 20 and ACR 50).*
- *Further guidance development is needed for long term outcomes in RA.*
- *As a reflection of signs and symptoms, clinical trials of 2 year duration may not be necessary to define improvement in physical function and durability of response. Trials of 6-12 months duration may provide enough evidence to support a claim for improvement in physical function.*
- *The claim improvement in physical function should be separated from claim* [redacted]
- *In the situation where high number of droupouts are inevitable, different imputation methods need to be considered other than LOCF.*
- *The data submitted by the Sponsor is robust to support the approval of leflunomide efficacy in improving the physical function.*

- *This reviewer recommends the **approval of the claim** for improved physical function to the label for ARAVA (leflunomide).*

Recommendations for regulatory action: Approved.

VIII. Appendix

#1-HAQ instrument
#2- Dr. Kent Johnson's draft executive review (dated 2000)
#3- Dr. Suktae Choi statistical reviews (dated 2000 and 2003)

Tatiana Oussova, MD (Medical Officer)

Lawrence Goldkind, Deputy Division Director
DAAODP, HFD-550

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-905 / S-006
20-905 / S-007

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

NEW DRUG APPLICATION

CLINICAL STUDIES

NDA/Serial Number:	20-905 / SE006
Drug Name:	AVARA™ (leflunomide 20 mg)
Indication(s):	Physical Function in RA
Applicant:	Aventis Pharmaceuticals, Inc.
Dates:	Received: December 13, 2002
Review Priority:	Priority review
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistics Reviewer:	Suktae Choi, Ph.D.
Concurring Reviewers:	Stan Lin, Ph.D.
Medical Division:	Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products (HFD-550)
Clinical Team:	Tatiana Oussova, M.D.
Project Manager:	Jane Dean

Keywords: missing data, dropout, sensitivity analysis, physical function

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This NDA supplement showed evidence of efficacy in favor of ARAVA™ 20 mg in comparison to placebo at 6 month in two studies (US301, MN301) and at 1 year in one-study (US301). This evidence is supported from the data of HAQ (US301, MN301), MHAQ (US301), and SF36 (US301). The corresponding results for 2 years were not conclusive because of high dropout rate for the 2 year data. An important review issue was the use of LOCF for missing data due to dropouts. This reviewer assessed this bias of the LOCF imputation approach by sensitivity analyses.

1.2 Brief Overview of Clinical Studies

Three two-year studies were reviewed for physical function indication, one U.S. study (US301), and two European studies (MN/301/303/305, MN/302/304). This NDA was originally submitted in June, 2000 for the indication of [redacted] withdrawn in December, 2000, and resubmitted with identical contents in December, 2002 for physical function indication. During their first submission, analysis results at two years were reviewed, and concluded as failure in showing efficacy for statistical review because of high rate of dropouts for all three studies. Details for the analyses of two years are in the appendix B. Therefore, this review will focus only on the analysis at one year and at six month. Following table shows a brief summary of design of three studies.

Table 1: Designs of studies; US301, MN/301/303/305, MN/302/304

	US301	MN/301/303/305 [a]	MN/302/304 [b]
Design	Double-blind, randomized, parallel group design	Double-blind, randomized, parallel group design	Double-blind, randomized, parallel group design
Location	United States		
Duration	2 years	2 years	2 years
Treatment groups (randomized)	leflunomide [c] (190) placebo [c] (128) methotrexate [c] (190)	leflunomide (133) Placebo/sulfasalazine [d] (92) sulfasalazine (133)	leflunomide (501) methotrexate (498)
Variables reviewed	HAQ DI, Modified HAQ, SF-36	HAQ mean	HAQ mean

a. MN301 was planned for 6 month. This study was extended additional 6 month, this extended period was named as MN303. Then it was extended another 1 year, and this period was named as MN305. MN/301/303/305 is a combination of these three phases with two years overall.
b. Similarly, MN302 was planned for 1 year, and it was extended additional 1 year, named MN304. MN/302/304 is the combination of these two phases with two years overall.
c. Non-responders were allowed to switch the treatments at 16 weeks. placebo and methotrexate treated subjects were switched to leflunomide, and leflunomide treated subjects were switched to methotrexate. In the primary analyses, switched subjects were considered as dropout.
d. All the placebo subjects were switched to sulfasalazine at 6 month.

Sponsor used ANOVA with LOCF for comparison of efficacy variables (change from baseline) between treatment groups. However sponsor's analyses excluded patients who does not have baseline or post baseline observations from their ITT analysis. For study US301, 28 subjects were excluded from all the efficacy analyses. Therefore, the sponsor's ITT is not a true ITT. Following table is the efficacy analysis results calculated by this reviewer based on true ITT and observed cases for placebo controlled studies.

Table 2: Efficacy results at 6 month and 1 year; Placebo control studies, ITT, LOCF

Study	Variable	Month	Treatment group	ITT			observed Case
				N	Mean (Std err)	P-value lef vs. pbo	N (%)
US301	HAQ DI	6	leflunomide	190	-0.379 (0.038)	<0.0001	175 (92%)
			placebo	128	-0.080 (0.046)		121 (95%)
			methotrexate	190	-0.218 (0.038)		176 (93%)
		12	leflunomide	190	-0.407 (0.039)	<0.0001	119 (63%)
			placebo	128	-0.062 (0.047)		56 (44%)
			methotrexate	190	-0.247 (0.039)		125 (66%)
	M-HAQ	6	leflunomide	190	-0.311 (0.035)	<0.0001	125 (66%)
			placebo	128	0.040 (0.042)		58 (45%)
			methotrexate	190	-0.186 (0.035)		129 (68%)
		12	leflunomide	190	-0.289 (0.036)	<0.0001	101 (53%)
			placebo	128	0.062 (0.044)		39 (30%)
			methotrexate	190	-0.140 (0.036)		106 (56%)
	SF-36	6	leflunomide	190	5.616 (0.640)	<0.0001	145 (76%)
			placebo	128	0.573 (0.780)		90 (70%)
			methotrexate	190	3.816 (0.640)		147 (77%)
		12	leflunomide	190	5.739 (0.668)	<0.0001	108 (57%)
			placebo	128	0.374 (0.814)		48 (38%)
			methotrexate	190	3.214 (0.668)		115 (61%)
MN301	HAQ Mean	6	leflunomide	133	-0.438 (0.040)	<0.0001	116 (87%)
			placebo	92	0.015 (0.048)		81 (88%)
			sulfasalazine	133	-0.244 (0.040)		113 (85%)

As shown in the table, analysis results for every variables showed significant results between leflunomide and placebo treated groups when LOCF was used. However, the dropout rates are very high for US301. One of the important reason of the high rate of dropout was from the design. US301 allowed the non-responders to switch their treatment at 16 week (4 month). See Table 1, Table Footnote c. This switching was considered as drop out in the efficacy analyses. This time point is not too far from 6 month, so that LOCF method at 6 month is acceptable. However, LOCF at 12 month is too far from 4 month, so that potential bias using LOCF need to be examined. For this purpose, sensitivity analyses were done by this reviewer, and the results supported the separation between two treatment groups. The methods and results of these sensitivity analyses are in the following section.

1.3 Statistical Issues and Findings

The major issue of this NDA is the high rate of missing data due to dropouts. Among the three

submitted controlled studies, only US301 was a placebo controlled study with at least one year duration. However, the dropout rate was for US301 much higher than other studies because of the allowance of switching treatment for non-responders at 16 week (See Table 2 in the previous section). The sponsor's analyses used LOCF to impute these missing data, they showed significant differences between leflunomide and placebo treated groups for all three variables at 6 month and 1 year. Since the many of the missing subjects were dropout at 16 week (4 month), the bias of LOCF at 12 month may be serious. Therefore, checking the sensitivity of the analysis results using LOCF at year 1 for US301 becomes very important. Following sensitivity analysis were performed by this reviewer.

- Observed case analyses

This is the same analyses with sponsor's primary analyses, but the population are the subjects who had the efficacy variable at the correspondent time point instead of ITT. The results are in the Table 3 below. As shown in the table, the separation between leflunomide and placebo treated groups are preserved for all three variables. This method is considered conservative because the power decreases when there is a positive effect size, and more subjects in placebo treated group are dropped out due to lack of efficacy. However, if the drop out due to AE is related to efficacy, in other words, if the unobserved missing efficacy data due to AE are less effective than observed data in drug efficacy, the difference between treatment will be overestimated, because the dropout rate due to AE will be higher in leflunomide treated group than the one in placebo treated group.

Table 3: Observed Case efficacy results at 1 year; Placebo controlled studies

Study	Variable	Month	Treatment group	Observed Case [a]		
				N	Mean (Std err)	P-value lef vs. pbo
US301	HAQ DI	12	leflunomide	119	-0.571 (0.051)	<0.0001
			placebo	56	-0.165 (0.074)	
			methotrexate	125	-0.384 (0.049)	
	M-HAQ	12	leflunomide	101	-0.438 (0.046)	0.0127
			placebo	39	-0.218 (0.074)	
			methotrexate	106	-0.248 (0.045)	
	SF-36	12	leflunomide	108	9.833 (0.996)	<0.0001
			placebo	48	2.619 (1.493)	
			methotrexate	115	7.394 (0.965)	

a. Observed Case includes the subjects who has observed variables at the time point.

As shown in the Table 3, the separation between leflunomide and placebo treated groups are preserved for all three variables. Therefore, the observed case analysis results support LOCF analysis at 12 month.

- Cross Imputing Analyses

This cross imputing analysis was used on the x-ray data in the original NDA by the statistical reviewer. In this submission, it can be applied to the variables for US301 at 12 months in comparison between leflunomide and placebo treated groups. The method is as follow; for missing

subjects for leflunomide treated group, impute from completers of placebo treated group, and for missing subjects for placebo treated group, impute from completers of leflunomide treated group. However, the missing rates are too high (more than 50%) in this case that we know this analysis is not possible to show separation between treatment without any calculation. Therefore, this analysis was failed to support LOCF analysis.

- Modified Cross Imputing Analyses

This analysis uses the same imputation method with cross imputing except the subjects who dropped out due to lack of efficacy. For the subjects who dropped out due to lack of efficacy, LOCF was used, and for the subjects who dropout due to other reasons, imputed from randomly selected values from completers of opposite treatment group. This method is reasonable under the assumption that the dependent structure between dropout and efficacy are same for both treatment groups. In other words, we assume the chance to dropout due to lack of efficacy is same between treatment groups with same amount of efficacy. Since this analysis method includes random selection, each trial will give different results. Following table shows the analysis results from ten independent trials.

Table 4: Modified cross imputing analysis results; US301, 12 month

	HAQ DI				MHAQ		
Trial	Mean Leflunomide	Mean Placebo	P-value	Trial	Leflunomide	Placebo	P-value
1	-0.3786	-0.1132	<0.0001	1	-0.1914	0.0273	0.0004
2	-0.3437	-0.1611	0.0047	2	-0.2039	0.0225	0.0003
3	-0.3483	-0.1406	0.0010	3	-0.2224	-0.0176	0.0005
4	-0.3674	-0.1377	0.0004	4	-0.2059	0.0254	0.0002
5	-0.3286	-0.0945	0.0003	5	-0.1836	-0.0264	0.0157
6	-0.3260	-0.1656	0.0132	6	-0.1921	-0.0010	0.0019
7	-0.3542	-0.1082	0.0001	7	-0.1750	-0.0049	0.0064
8	-0.3496	-0.1445	0.0011	8	-0.2132	-0.0215	0.0025
9	-0.3418	-0.1405	0.0012	9	-0.1961	-0.0049	0.0015
10	-0.3365	-0.1307	0.0013	10	-0.2263	-0.0166	0.0006

As shown in the table, all the trials still showed the significant differences. Therefore, this modified cross imputing analysis supports LOCF at 12 month.

- As Randomized (including measurements after treatment switching)

As mentioned above, US301 allowed the non-responders to switch their treatment groups and considered as dropout at 16 weeks. However, after the subjects switched their treatment, they keep measured the efficacy variables. In this analyses, we include the efficacy observations after the switching of their treatments, but the treatment group is as randomized. In other words, if a subject was randomized as placebo group but switched to leflunomide group at 16 week, all the efficacy observations (including the observations after the switching treatment) are considered placebo treatment group as randomized. This analysis was done for MHAQ only because data of other variables were not available for this analysis. By using this method, the 1 year completer rates for MHAQ are increased (leflunomide: 125 (65.8%), placebo: 95 (74.3%), methotrexate: 140 (74.5%)).

For the missing data (dropout before 1 year), LOCF was used, Since the completer's rate is increased, the bias due to LOCF would be decreased. Also, this method is conservative because placebo group includes the observations with leflunomide treated subjects. The following table summarizes the result of this analysis.

Table 5: As randomized analysis results of MHAQ at year 1; US301, LOCF

(N) Mean (Stderr)			P-values		
leflunomide	placebo	methotrexate	leflunomide vs. placebo	leflunomide vs. methotrexate	methotrexate vs. placebo
(N=190) -0.275 (0.037)	(N=128) -0.094 (0.045)	(N=188) -0.178 (0.038)	0.0022	0.0671	0.1567

As shown, leflunomide group and placebo group are still significantly different. The placebo group shows better efficacy for this analysis (mean –0.094) than for the original LOCF (mean 0.062). In the other hand, the mean for leflunomide in this analysis (-0.275) is worse than the mean for original LOCF analysis (-0.289), this difference is from the effect of the observations during the methotrexate treated period. Therefore, we can see the conservative of this sensitivity analysis. This sensitivity analysis supports LOCF at 12 month.

2. INTRODUCTION

2.1 Overview

Three two-year studies were reviewed for physical function indication, which are one U.S. study (US301), and two European studies (MN/301/303/305, MN/302/304). This NDA was originally withdrawn in December, 2000, and resubmitted with identical contents in December, 2002 for physical function indication. During their first submission, analysis results at two years were reviewed, and concluded as failure in showing efficacy for statistical review because of high rate of dropouts for all three studies. Details for the analyses of two years are in the appendix B. Therefore, this review will focus only on the analysis at one year and at six month. Following table shows a brief summary of design of three studies.

Table 6: Designs of studies; US301, MN/301/303/305, MN/302/304

	US301	MN/301/303/305 [a]	MN/302/304 [b]
Design	Double-blind, randomized, parallel group design	Double-blind, randomized, parallel group design	Double-blind, randomized, parallel group design
Location	United States		
Duration	2 years	2 years	2 years
Treatment groups (randomized)	leflunomide [c] (190) placebo [c] (128) methotrexate [c] (190)	leflunomide (133) Placebo/sulfasalazine [d] (92) sulfasalazine (133)	leflunomide (501) methotrexate (498)
Variables reviewed	HAQ DI, Modified HAQ, SF-36	HAQ mean	HAQ mean

a. MN301 was planned for 6 month. This study was extended additional 6 month, this extended period was named as MN303. Then it was extended another 1 year, and this period was named as MN305. MN/301/303/305 is a combination of these three phases with two years overall.

b. Similarly, MN302 was planned for 1 year, and it was extended additional 1 year, named MN304. MN/302/304 is the combination of these two phases with two years overall.

c. Non-responders were allowed to switch the treatments at 16 weeks. placebo and methotrexate treated subjects were switched to leflunomide, and leflunomide treated subjects were switched to methotrexate. In the primary analyses, switched subjects were considered as dropout.

d. All the placebo subjects were switched to sulfasalazine at 6 month.

As shown in the table, only US301 is a placebo controlled study all the time, and MN301 was a placebo controlled study for six month. Therefore, this review is focused only for these two studies.

2.2 Data Sources

The sponsor submitted and withdrawn in 2000, then resubmitted in the end of 2002. Following are

the location of electric files.

- NDA 20-905 SE/006 submission (12/13/2002)

  Final Reports: hard copies and CDs

  Data set: \\Cdsesub1\n20905\S_006\2002-12-30\SAS Dataset Files

- Additional submission requested by division (requested 12/18/2002, received 2/24/2003)

  Analysis results: E-mail through project manager

  Data set: E-mail through project manager

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Primary efficacy analyses

For physical function indication, HAQ, MHAQ, and SF-36 were reviewed as primary efficacy variables. Sponsor used ANOVA with LOCF for comparison of these variables (change from baseline) between treatment groups. However sponsor's analyses excluded patients who does not have baseline or post baseline observations from their ITT analysis. For example, for study US301, 28 subjects were excluded from all the efficacy analyses among 508 randomized subjects. Therefore, the sponsor's ITT is not a true ITT. Following table is the efficacy analysis results calculated by this reviewer based on true ITT and observed cases for placebo controlled studies.

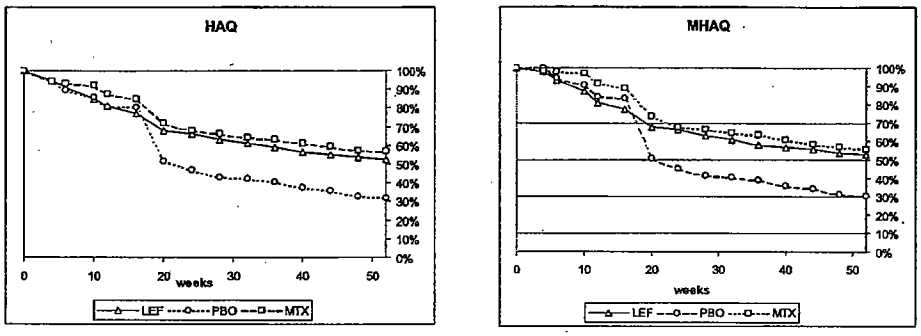
Table 7: Efficacy results at 6 month and 1 year; Placebo control studies, ITT, LOCF

Study	Variable	Month	Treatment group	ITT			observed Case [a]
				N	Mean (Std err)	P-value lef vs. pbo	N (%)
US301	HAQ DI	6	leflunomide	190	-0.379 (0.038)	<0.0001	175 (92%)
			placebo	128	-0.080 (0.046)		121 (95%)
			methotrexate	190	-0.218 (0.038)		176 (93%)
		12	leflunomide	190	-0.407 (0.039)	<0.0001	119 (63%)
			placebo	128	-0.062 (0.047)		56 (44%)
			methotrexate	190	-0.247 (0.039)		125 (66%)
	M-HAQ	6	leflunomide	190	-0.311 (0.035)	<0.0001	125 (66%)
			placebo	128	0.040 (0.042)		58 (45%)
			methotrexate	190	-0.186 (0.035)		129 (68%)
		12	leflunomide	190	-0.289 (0.036)	<0.0001	101 (53%)
			placebo	128	0.062 (0.044)		39 (30%)
			methotrexate	190	-0.140 (0.036)		106 (56%)
	SF-36	6	leflunomide	190	5.616 (0.640)	<0.0001	145 (76%)
			placebo	128	0.573 (0.780)		90 (70%)
			methotrexate	190	3.816 (0.640)		147 (77%)
		12	leflunomide	190	5.739 (0.668)	<0.0001	108 (57%)
			placebo	128	0.374 (0.814)		48 (38%)
			methotrexate	190	3.214 (0.668)		115 (61%)
MN301	HAQ Mean	6	leflunomide	133	-0.438 (0.040)	<0.0001	116 (87%)
			placebo	92	0.015 (0.048)		81 (88%)
			sulfasalazine	133	-0.244 (0.040)		113 (85%)

a. Observed Case includes the subjects who has observed variables at the time point.
For US301, HAQ DI and SF36 were observed at baseline, at 6 month, and at 12 month, or when they dropout. For HAQ DI and SF-36, the observed case at 6 months includes subjects who has observation between baseline and 6 month as well as at 6 month. Similarly, the observed case at 12 month includes subjects who has observation between 6 month and 12 month as well as at 12 month.

As shown in the table, analysis results for all the variables showed significant difference between leflunomide and placebo treated groups when LOCF was used. However, the dropout rates are very high for US301. One of the important reason of the high rate of dropout was from the design. US301 allowed the non-responders to switch their treatment at 16 week (4 month). The placebo treated subjects were switched to their treatment to leflunomide, leflunomide treated subjects were to methotrexate, and the methotrexate were to leflunomide. This switching was considered as drop out in the primary efficacy analyses. Following figure shows the percentage of subjects who are remained in the study over time. The remainder is define that the subject who has at least one observation after the time point. So that the remainder is defined for each variable and each time point.

Figure 1: Percentage of remainders in the study over the time; US301



As shown in the figure, there are big drops at 16 weeks. Since the switching time point is not too far from 6 month, and the dropout rates are not too low, LOCF method at 6 month can be rational. However, since LOCF at 12 month is too far from 4 month, and dropout rates are too high, the potential bias using LOCF need to be examined. For this purpose, sensitivity analyses were done by this reviewer, and the results supported the separation between two treatment groups. The methods and results of these sensitivity analyses are in the following section.

3.1.2 Sensitivity Analyses

The major issue of this NDA is the high rate of missing data due to dropouts. Among the three submitted controlled studies, only US301 was a placebo controlled study with at least one year duration. However, the dropout rate for US301 was much higher than other studies because of the allowance of switching treatment for non-responders at 16 week. The sponsor's analyses used LOCF to impute these missing data, they showed significant differences between leflunomide and placebo treated groups for all three variables at 6 month and 1 year. Since the majority missing subjects for 6 month were dropout at 16 week (4 month) and the missing rate is common, LOCF at 6 month is considered as rational. However, it is different at 12 month. The dropout rate is high itself, and many of them were

dropped out in early stage. (See Figure 1). Therefore, examining the sensitivity of the analysis results using LOCF at year 1 for US301 is very important to determine the efficacy of this drug for physical function indication. Following sensitivity analyses were performed by this reviewer.

- Observed case analyses

This is the same analyses with sponsor's primary analyses, but the population are the subjects who had the efficacy variable at the correspondent time point instead of ITT. The results are in the Table 8 below. As shown in the table, the separation between leflunomide and placebo treated groups are preserved for all three variables. This method is considered conservative because the power decreases when there is a positive effect size, and more proportion of dropout due to lack of efficacy for placebo treated group than active groups However, if the unobserved missing efficacy data due to AE are less effective than observed data in drug efficacy, the difference between treatment will be overestimated, because the dropout rate due to AE will be higher in leflunomide treated group than the one in placebo treated group.

Table 8: Observed Case efficacy results at 1 year; Placebo controlled studies

Study	Variable	Month	Treatment group	Observed Case [a]		
				N	Mean (Std err)	P-value lef vs. pbo
US301	HAQ DI	12	leflunomide	119	-0.571 (0.051)	<0.0001
			placebo	56	-0.165 (0.074)	
			methotrexate	125	-0.384 (0.049)	
	M-HAQ	12	leflunomide	101	-0.438 (0.046)	0.0127
			placebo	39	-0.218 (0.074)	
			methotrexate	106	-0.248 (0.045)	
	SF-36	12	leflunomide	108	9.833 (0.996)	<0.0001
			placebo	48	2.619 (1.493)	
			methotrexate	115	7.394 (0.965)	

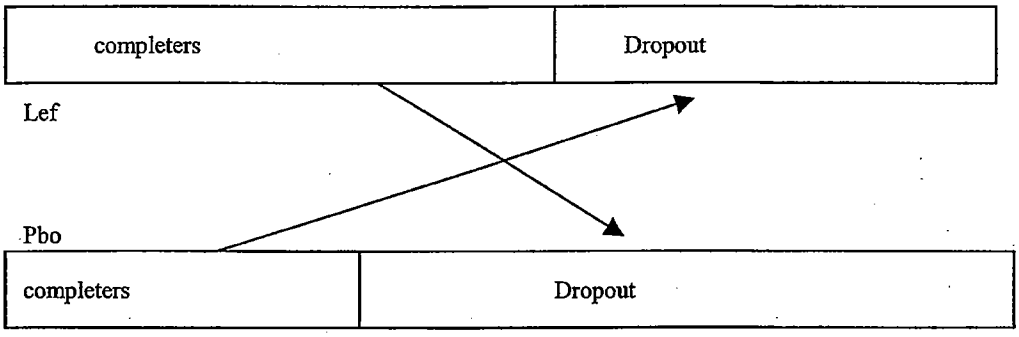
a. Observed Case includes the subjects who has observed variables at the time point.

As shown in the Table 3, the separation between leflunomide and placebo treated groups are preserved for all three variables. Therefore, the observed case analysis results support LOCF analysis at 12 month.

- Cross Imputing Analyses

This cross imputing analysis was used on the x-ray data in the original NDA by the statistical reviewer. In this submission, it can be applied to the variables for US301 at 12 months in comparison between leflunomide and placebo treated groups. The method is as follow; for missing subjects for leflunomide treated group, impute from completers of placebo treated group, and for missing subjects for placebo treated group, impute from completers of leflunomide treated group. See the following figure.

Figure 2: Imputation method for Cross Imputing Analysis

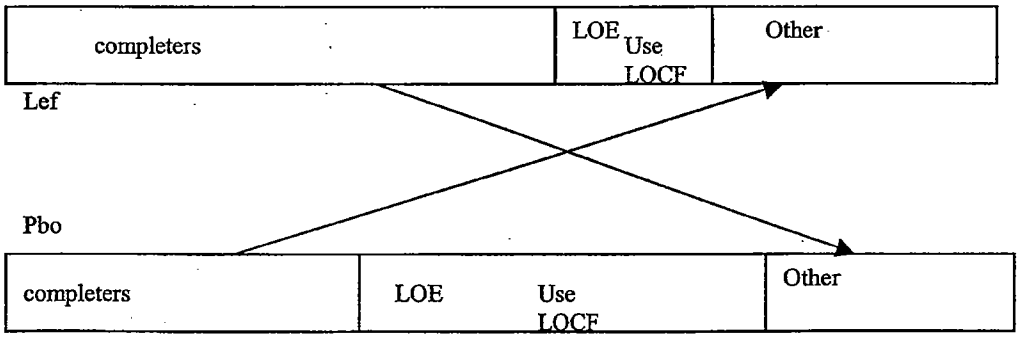


However, the missing rates are too high (more than 50%) in this case that we know this analysis is not possible to show separation between treatment without any calculation. Therefore, this analysis was failed to support LOCF analysis.

- Modified Cross Imputing Analyses

This analysis uses the same imputation method with cross imputing except the subjects who dropped out due to lack of efficacy. For the subjects who dropped out due to lack of efficacy, LOCF was used, and for the subjects who dropout due to other reasons, imputed from randomly selected values from completers of opposite treatment group.

Figure 3: Imputation method for Modified Cross Imputing Analysis



This method is reasonable under the assumption that the dependent mechanism between dropout and efficacy are same for both treatment groups. In other words, we assume the chance to dropout due to lack of efficacy is same between treatment groups with same amount of efficacy. Following table shows the descriptive statistics of HAQ and MHAQ by dropout reasons.

Table 9: HAQ and MHAQ scores changed from baseline by the reasons of dropout

Variable	Treatment	N	Completers		Dropout due to LOE		Dropout due to other	
			N (%)	Mean (stderr)	N (%)	Mean (stderr)	N (%)	Mean (stderr)
HAQ	leflunomide	190	99 (52.1%)	-0.622 (0.057)	31 (16.3%)	-0.039 (0.077)	60 (31.6%)	-0.320 (0.070)
	placebo	128	40 (31.3%)	-0.231 (0.089)	61 (47.7%)	0.078 (0.056)	27 (21.1%)	-0.113 (0.102)
	methotrexate	190	107 (56.9%)	-0.393 (0.055)	42 (22.3%)	0.064 (0.066)	39 (20.7%)	-0.242 (0.087)
MHAQ	leflunomide	190	101 (53.2%)	-0.438 (0.046)	31 (16.3)	0.008 (0.076)	58 (30.5%)	-0.186 (0.068)
	placebo	128	39 (30.5%)	-0.218 (0.074)	62 (48.4%)	0.270 (0.053)	27 (21.1%)	-0.013 (0.099)
	methotrexate	190	106 (55.8%)	-0.248 (0.045)	44 (23.2%)	0.155 (0.063)	40 (21.1%)	-0.179 (0.816)

As shown in the table, the mean change from baseline between leflunomide and placebo are similar for the subjects dropout due to lack of efficacy. This fact make us comfortable to use this modified cross imputing analysis. Since this analysis method includes random selection, each trial will give different results. Following table shows the analysis results from ten independent trials.

Table 10: Modified cross imputing analysis results; US301, 12 month

	HAQ DI				MHAQ		
Trial	Leflunomide	Placebo	P-value	Trial	Leflunomide	Placebo	P-value
1	-0.3786	-0.1132	<0.0001	1	-0.1914	0.0273	0.0004
2	-0.3437	-0.1611	0.0047	2	-0.2039	0.0225	0.0003
3	-0.3483	-0.1406	0.0010	3	-0.2224	-0.0176	0.0005
4	-0.3674	-0.1377	0.0004	4	-0.2059	0.0254	0.0002
5	-0.3286	-0.0945	0.0003	5	-0.1836	-0.0264	0.0157
6	-0.3260	-0.1656	0.0132	6	-0.1921	-0.0010	0.0019
7	-0.3542	-0.1082	0.0001	7	-0.1750	-0.0049	0.0064
8	-0.3496	-0.1445	0.0011	8	-0.2132	-0.0215	0.0025
9	-0.3418	-0.1405	0.0012	9	-0.1961	-0.0049	0.0015
10	-0.3365	-0.1307	0.0013	10	-0.2263	-0.0166	0.0006

As shown in the table, all the trials still showed the significant differences. Therefore, this modified cross imputing analysis supports LOCF at 12 month.

- As Randomized (including measurements after treatment switching)

As mentioned above, US301 allowed the non-responders to switch their treatment groups and considered as dropout at 16 weeks. However, after the subjects switched their treatment, they restart to measure the efficacy variables. In this analyses, we include the efficacy observations after the switching of their treatments, but the treatment group is as

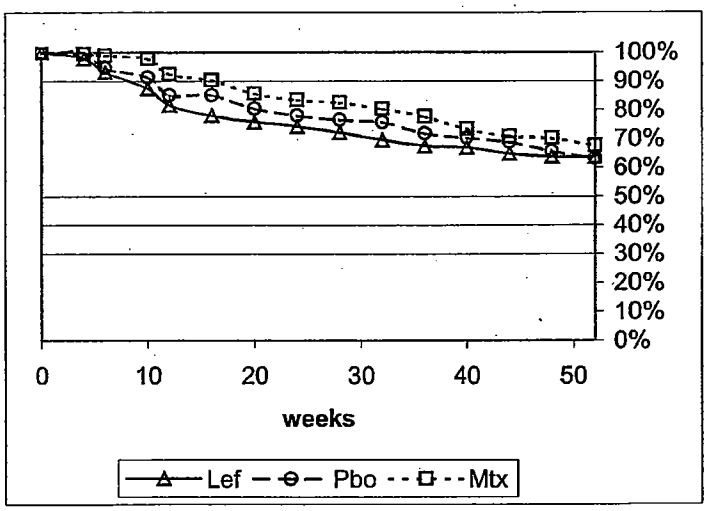
randomized. In other words, if a subject was randomized as placebo group but switched to leflunomide group at 16 week, all the efficacy observations (including the observations after the switching treatment) are considered placebo treatment group as randomized. This analysis was done for MHAQ only because data of other variables were not available for this analysis.

Table 11: Decomposition of patients

	Total	Completers	Switched treatment / observation at 1yr	Drop out before 1yr
Lef	190	101 (53.2%)	24 (12.6%)	65 (34.2%)
Pbo	128	39 (30.5%)	56 (43.8%)	33 (25.8%)
Mtx	188	106 (56.4%)	34 (18.1%)	48 (25.5%)

As shown, including "Switched treatment/observation at 1yr" column, almost 60% to 70% of the subjects have MHAQ observations at 52 week, and also drop out time shifted to later as shown in the following figure.

Figure 4: Percentage of remainders including treatment switched subjects; MHAQ US301



For the missing data (dropout before 1 year), LOCF was used in the analysis. Since the completer's rate is increased and the dropout time is delayed, the bias due to LOCF would be decreased. Also, a new bias introduced in this analysis is conservative because placebo group includes the observations with leflunomide treated subjects. The following table summarizes the result of this analysis.

Table 12: As randomized analysis results of MHAQ at year 1; US301, LOCF

(N) Mean (Stderr)			P-values		
leflunomide	placebo	methotrexate	leflunomide vs. placebo	leflunomide vs. methotrexate	methotrexate vs. placebo
(N=190) -0.275 (0.037)	(N=128) -0.094 (0.045)	(N=188) -0.178 (0.038)	0.0022	0.0671	0.1567

As shown, leflunomide group and placebo group are still significantly different. The placebo group shows better efficacy for this analysis (mean –0.094) than for the original LOCF (mean 0.062). In the other hand, the mean for leflunomide in this analysis (-0.275) is worse than the mean for original LOCF analysis (-0.289), this difference is from the effect of the observations during the methotrexate treated period. Therefore, we can see the conservative of this sensitivity analysis. This sensitivity analysis supports LOCF at 12 month.

3.2 Evaluation of Safety

Safety data were not reviewed

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Additional analyses including gender, age, treatment group, and their interactions as factors were performed by this reviewer for HAQ, MHAQ, and SF-36 at 6 month and 12 month using LOCF. None of them showed significant results for interactions between treatment group vs. gender or between treatment group vs. age. No further issues were found.

4.2 Other Special/Subgroup Populations

No further subgroup analysis were performed. In the review of these two studies,

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The most critical issue in this review was missing data. This reviewer focused on the comparison between leflunomide and placebo at 6 month and 12 month. Since the remainders in each treatment group were too low and early, the protocol specified imputation method (LOCF) had to be examined for its validity especially at 12 month. Three different sensitivity analyses were done by this reviewer, and all of them supported the results of LOCF at 12 month, which showed significant difference between two treatment groups. Details of the analysis results are in the Table 7 in previous section.

5.2 Conclusions and Recommendations

Among three studies for physical function indication, only two studies (US301, MN301) had placebo control. The review of these two study concludes that this NDA supplement showed the evidence of the separation of HAQ (Health Assessment Questionnaire), MHAQ (Modified HAQ), and SF-36 between ARAVA™ 20 mg treated group and placebo treated group at 6 month (from two studies) and at 1 year (from one study). However, for the efficacy observations at two year, none of the analyses showed robust results. The sponsor's analysis results for two year were not enough to conclude because of the high rate of missing data due to early dropouts.

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/s/

Suktae Choi
6/6/03 04:57:55 PM
BIOMETRICS

Stan Lin
6/6/03 05:01:32 PM
UNKNOWN

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-905 / S-006
20-905 / S-007

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

16. DEBARMENT CERTIFICATION

Aventis Pharmaceuticals Inc. hereby certifies that we did not and will not use in any capacity the services of any person debarred under Section 306 (a) or (b) in connection with this application.

6/6/00

J. Michael Nicholas, Ph.D.
Vice President
U.S. Drug Regulatory Affairs
Aventis Pharmaceuticals Inc.

Date

NDA 20-905
Leflunomide Tablets

CONFIDENTIAL

Hoechst Marion Roussel

Hoechst Marion Roussel, Inc.
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Telex: 214520

26 February 1998

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parklawn Drive
Rockville, MD 20857

Subject: Re: Original NDA Submission (20-905) for Leflunomide Tablets
Patent Information and Declaration

Dear Sir:

The undersigned submits that the following patent information is relevant to Leflunomide Tablets:

PATENT NUMBER(S):	United States Patent No. 4,284,786
EXPIRATION DATE(S):	December 13, 1999, under the provisions of Uruguay Pact of the General Agreement on Tarrifs and Trade ("GATT")
PATENT OWNER:	Hoechst Aktiengesellschaft 65926 Frankfurt am Main Germany
TYPE OF PATENT:	Drug Substance

The undersigned declares that United States Patent No. 4,284,786 covers leflunomide, the drug substance of the drug product for which the above-referenced NDA is being submitted for approval for use in treating rheumatoid arthritis, and also covers both the drug product (formulation) containing the drug substance and methods of using said drug substance in treating rheumatoid arthritis. The patent has not been extended under 35USC156.

Two copies of this declaration are submitted herewith. Please list the above patent in the Orange Book Publication upon approval of the NDA.

Cusmitted by:

Gary D. Street
Vice President
Hoechst Marion Roussel, Inc.
Patent Department

Hoechst

Hoechst Marion Roussel
The Pharmaceutical Company of Hoechst

Hoechst Marion Roussel

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26 February 1998

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Center for Drug Evaluation and Research
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Park Bldg., Room 2-14
12420 Parklawn Drive
Rockville, MD 20857

Subject: Re: Original NDA Submission (20-905) for Leflunomide Tablets
Patent Information and Declaration

Dear Sir:

The undersigned submits that the following patent information is relevant to Leflunomide Tablets:

PATENT NUMBER(S):	United States Patent No. 4,351,841
EXPIRATION DATE(S):	December 13, 1999, under the provisions of Uruguay Pact of the General Agreement on Tariffs and Trade ("GATT")
PATENT OWNER:	Hoechst Aktiengesellschaft 65926 Frankfurt am Main Germany
TYPE OF PATENT:	Drug Product (formulation) and Method of Use

The undersigned declares that United States Patent No. 4,351,841 covers the drug product (formulation) containing the drug substance leflunomide and a method of using said drug substance and said drug product in treating rheumatoid arthritis. The patent has not been extended under 35USC156.

Two copies of this declaration are submitted herewith. Please list the above patent in the Orange Book Publication upon approval of the NDA.

Submitted by:

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26 February 1998

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Park Bldg., Room 2-14
12420 Parklawn Drive
Rockville, MD 20857

Subject: Re: Original NDA Submission (20-905) for Leflunomide Tablets
Patent Information and Declaration

Dear Sir:

The undersigned submits that the following patent information is relevant to Leflunomide Tablets:

PATENT NUMBER(S):	United States Patent No. 5,679,709
EXPIRATION DATE(S):	October 21, 2014
PATENT OWNER:	Hoechst Aktiengesellschaft 65926 Frankfurt am Main Germany
TYPE OF PATENT:	Method of Use

The undersigned declares that United States Patent No. 5,679,809 covers a metabolite of leflunomide and a method of using drug substance (leflunomide) and drug product (formulation) containing said drug substance in treating rheumatoid arthritis. United States Patent 5,679,709 has not been extended under 35USC156.

Two copies of this declaration are submitted herewith. Please list the above patent in the Orange Book Publication upon approval of the NDA.

Submitted by:

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Hoechst

Hoechst Marion Roussel
The Pharmaceutical Company of Hoechst

EXCLUSIVITY SUMMARY for NDA # 20-905_____ SUPPL # 006

Trade Name: Arava™_____ Generic Name: leflunomide

Applicant Name: Aventis Pharmaceuticals Inc._____ HFD-550

Approval Date: June 13, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_**X**_/

   b) Is it an effectiveness supplement? YES /_**X**_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? **SE1**

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_**X**_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name:

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_ **X** _/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # **20-905**

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_**X**_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_**X**_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # **US 301**

Investigation #2, Study # **MN 301/303/305**

Investigation #3, Study # **MN 302/304**

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_**X**_/

Investigation #2 YES /___/ NO /_**X**_/

Investigation #3 YES /___/ NO /_**X**_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_**1**_, Study # **US 301**

Investigation #_**2**_, Study # **MN 301/303/305**

Investigation #_**3**_, Study # **MN 302/304**

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # — ES /_X_/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Jane A. Dean, RN, MSN — **June 17, 2003**
Signature of Preparer — Date
Title: **Project Manager**

Lee S. Simon, MD — **June 17, 2003**
Signature of Office or Division Director — Date

cc:
Archival NDA 20-905
HFD-550/Division File
HFD-550/J. Dean/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Lee Simon
6/27/03 12:16:06 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA # 20-905 Supplement Type (e.g. SE5): SE1 Supplement Number: 006

Stamp Date: December 13, 2002 Action Date: June 13, 2003

HFD-550 Trade and generic names/dosage form: Arava™ (leflunomide) tablets

Applicant: Aventis Pharmaceuticals Inc. Therapeutic Class: Antiinflammatory

Indication(s) previously approved: Rheumatoid Arthritis

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): One

Indication #1: Rheumatoid Arthritis

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.

NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns

- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies/Ongoing

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}
Jane A. Dean, RN, MSN
Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

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/s/

Jane Dean
6/12/03 07:09:54 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-905\S-006

INFORMATION REQUEST LETTER

Aventis Pharmaceuticals Inc.
Attention: Joseph Scheeren
US Regulatory Liaison
200 Crossing Blvd.
Mail Code BX2-209G
Bridgewater, NJ 08807

Dear Mr. Scheeren:

Please refer to your December 13, 2002 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arava (leflunomide) tablets, 10 mg, 20 mg, and 100 mg.

We are reviewing the Clinical Statistical sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please clarify whether the estimated yearly progression for the year two cohort was calculated with or without the year one changes incorporated into the numerator and the additional year of disease incorporated into the denominator;
2. Please explain differences in the x-ray data appearing in the tables found in the Augst 29, 2002 report sent to the FDA via email on September 9, 2002 and the resubmission of the efficacy supplement 6, submitted on December 13, 2002.

If you have any questions, please call Ms. Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Jane Dean
5/13/03 09:19:21 AM
For Carmen DeBellas

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NO FILING ISSUES IDENTIFIED

NDA 20-905/S-006

Aventis Pharmaceuticals
Attention: Michael D. Rozycki, PhD
US Regulatory Affairs
200 Crossing Blvd., Mail Code BX2-209G
Bridgewater, NJ 08807

Dear Dr. Rozycki:

Please refer to your December 13, 2002 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arava (leflunomide) Tablets, 10 mg, 20 mg and 100 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on February 13, 2003 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, please call Ms. Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, RPh
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Carmen DeBellas
5/8/03 12:34:32 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-905/S-007

PRIOR APPROVAL SUPPLEMENT

Aventis Pharmaceuticals
Attention: Jerry Klimek
Global Drug Regulatory Affairs
300 Somerset Corporate Boulevard
Bridgewater, New Jersey 08807-2854

Dear Mr. Klimek:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Arava (leflunomide) Tablets 10 mg, 20 mg, 100 mg

NDA Number: 20-905

Supplement Number: S-007

Date of Supplement: September 04, 2001

Date of Receipt: September 05, 2001

This supplemental application, submitted as "Changes Being Effected", proposes the following changes to the package insert for Arava (leflunomide) Tablets: to revise the ALT monitoring recommendation, to add post-marketing reports of hepatitis, jaundice/cholestaisis, severe liver injury such as hepatic failure and acute hepatic necrosis that may be fatal, as well as additional changes unrelated to the liver reports.

Changes of this kind **cannot** be put into effect prior to approval of a supplement. An approved supplement is required for these proposed changes prior to distributing drug product made with these changes.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
HFD-550
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
HFD-550
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call me at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Barbara Gould
Project Manager
Division of Anti-Inflammatory, Analgesic and Ophthalmic
Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Barbara Gould
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