Office of Clinical Pharmacology and Biopharmaceutics Review

NDA Number	20-905 (SE5-012)
Submission Date(s)	September 4th, 2003
Brand Name	Arava®
Generic Name	Leflunomide
Reviewer	Abimbola Adebowale Ph.D.
PM Reviewer	Jenny J. Zheng Ph.D.
Team Leader	Dennis Bashaw Pharm.D.
OCPB Division	DPE-III
OND division	HFD-550
Sponsor	Aventis Pharmaceuticals Inc., Bridgewater, NJ 08807-0890
Relevant IND(s)	41, 533
Submission Type; Code	Labeling Supplement with Pediatric Clinical Data, Submission of Pediatric Study Reports, Pediatric Exclusivity Determination Requested
Formulation; Strength(s)	Tablets; 10 mg, 20 mg, 100 mg
Indication	Juvenile Rheumatoid Arthritis

1. Executive Summary

This application consists of pediatric study reports for Arava®, to fulfill the requirements of a Written Request issued on March 30, 1999. The request was for pediatric information on the use of Arava® in the treatment of active polyarticular-course Juvenile Rheumatoid Arthritis (JRA). Several amendments were made to the original written request between December 6th, 2000 and July 9th, 2003. The final correspondence from the Agency approving the changes to the Written Request that was proposed by Aventis ® was dated July 9th 2003. The original NDA for Arava ® was approved on September 10th, 1998 with an indication in adults for active rheumatoid arthritis (RA). In this submission the applicant is asking for pediatric exclusivity and, labeling changes that includes pertinent pediatric data in two sections of the current approved package insert for Arava ® tablets. The FDA granted the pediatric exclusivity on November 10th, 2003.

The PK study proposed in the Written Request was to characterize steady state pharmacokinetics of leflunomide in children and adolescent (aged 3 to 17 years old) patients with a clinical diagnosis of polyarticular course JRA. Justification of the dose should be provided based on pharmacokinetic data. In addition to the primary analysis, a comparison to pharmacokinetic parameters in adult patients should be performed and, covariate analysis performed across gender, age and body weight in the target population.

The pharmacokinetics (PK) of leflunomide was investigated in two clinical efficacy and safety studies (Study 1037 and 3503). The pooled data was then evaluated using the

population (POPPK) approach. The objectives of the POPPK analysis were to characterize the steady state pharmacokinetics of the active metabolite (M1) of leflunomide in pediatric polyarticular JRA patients. In addition the individual PK parameters and exposure measures at steady-state in the pediatric JRA patients were compared to those of adult RA patients and the appropriate dose recommendations for use of leflunomide in pediatric patients were calculated to match the adult exposure data.

1.1 Recommendation:

The applicant has conducted an adequate population pharmacokinetic analysis (POPK) on the pooled data from two clinical studies, to characterize the pharmacokinetics of M1 (the active metabolite of leflunomide) in pediatric patients with polyarticular-course JRA ranging in age from 3 to 17 years old. The results of the population pharmacokinetic analysis demonstrated that children with body weights < 40 kg have a reduced clearance of M1 relative to children with body weights > 40 kg and, adult rheumatoid arthritis patients.

In the pivotal efficacy and safety study (# 3503), the mean systemic exposure for patients who weighed > 40 kg was comparable to that of adult RA patients. However, the mean steady state concentration (Css average) obtained in children with body weights < 20 kg was about 63 % lower than that of children who weighed > 40 kg. In addition the mean Css average for responders was about 31 % less than that obtained in non-responders, suggesting that a certain exposure may be required to obtain a response to treatment. [*The clinical division also observed that the response rate of leflunomide in children < 40 kg was less robust than in children with body weights greater than 40 kg*]. Therefore the exposure/response data suggests that the doses administered to the children who weighed < 20 kg may have been sub-optimal in spite of their reduced clearance which, normally would have resulted in increased plasma levels with matched doses.

Based on the PK data the applicant did include a refined leflunomide treatment regimen to increase the dose of leflunomide to about 100 and 50 % higher than that studied for children with bodyweights < 20 kg and between 20-40 kg. However, they have not requested for this proposed regimen to be included in the label. The clinical division has decided that due to the inadequacy of the efficacy and safety information provided by the applicant, this indication is not recommended in the pediatric population, therefore no dosing recommendations are proposed at this time.

The clinical division has, however, decided to include the limited efficacy and safety data obtained from the pediatric JRA clinical studies in the label. Consequently, from a clinical pharmacology and biopharmaceutics perspective the information provided is acceptable to meet the requirements of the pediatric written request. Provided that satisfactory agreement is reached between the applicant and the Agency, limited changes to the language in the package insert should be included to incorporate some of the pediatric pharmacokinetics information without allowing the indication at this time.

1.2 Phase IV Commitments: None were identified.

2. Summary of CPB Findings

Based on the pediatric written request and agreements between the FDA and Aventis, three studies were conducted and submitted in this NDA as follows:

- Study 1037 was an open-label, non-controlled, multi-center, Phase IB study over a 6-month treatment period with up to a 24-month extension phase.
- Study 3503 was a randomized, double blind, parallel group 16-week treatment trial comparing leflunomide to methotrexate, in pediatric subjects with polyarticular course JRA who were DMARD-therapy naïve.
- Study 3504 was an eight month extension of study 3503

Pharmacokinetics (PK) was investigated in pooled data from studies 1037 and 3503 and evaluated using the population (POPPK) approach. The objectives of the POPPK analysis were:

A. to establish a model that describes the pharmacokinetic characteristics of the active metabolite (M1) of leflunomide in the JRA population
B. to examine the influence of demographic covariates (i.e., sex, age, body weight, BSA) on the pharmacokinetics of M1 in the JRA population
C. to compare the POSTHOC estimates of individual PK parameters and exposure measures at steady-state in the pediatric JRA patients to those of adult RA patients
D. to determine appropriate dose recommendations for leflunomide use in the JRA population

The review of the data obtained from the POPPK analysis is summarized below:

Pharmacokinetics of M1 in JRA patients

In pediatric subjects with polyarticular course JRA, the pharmacokinetics of M1 (active metabolite of leflunomide) was well described by a one-compartment model with first order input similar to adult RA patients. There was also a wide inter-subject variability in CL/F observed in the pediatric patients similar to adult RA patients. However, results of a CL/F by weight evaluation of the POPPK data demonstrated that pediatric patients with polyarticular course JRA with body weights < 40 kg have a reduced clearance of M1 relative those with body weights > 40 kg (see table below) and, to adult RA patients (estimated clearance in current label = 31 ml/h)

Table 1 : Population Pharmacokinetic estimate of M1 for Clearance in pediatric patients with polyarticular course JRA Mean ±SD [Range]

N	Body Weight (kg)	CL (mL/h)
10	13-20	18 ± 9.8 [6.8-37]
30	20-40	18 ± 9.5 [4.2-43]
33	40-75	26 ± 16.0 [9.7-93.6]

In study 3503, the mean systemic exposure for patients who weighed > 40 kg was comparable to that of adult RA patients (mean Css = 34 mcg/mL). However, the dosage regimen studied produced lower mean systemic exposures in the pediatric patients who

weighed < 20 kg relative to the patients who weighed > 20 kg. The mean Css average in patients with body weights < 20 kg was about 63 % lower than that obtained in patients with body weights > 40 kg (see table below).

Table 2: Average Steady State Concentration (Css) Mean ± SD in pediatric patients with polyarticular course JRA in Study 3503

N	Body Weight (kg)	Studied Daily Dose in Study 3503	Css in Study 3503 (mcg/mL)
8	13-20	5	14.5 ± 7.2
19	20–40	10	30.0 ± 19.3
20	40-75	20	38.9 ± 20.4

The results of the comparison between exposure and response (employing the JRA 30 % definition of improvement (DOI) responder endpoint) demonstrated that there was a trend for lower exposures in the group of patients who failed to respond to leflunomide. The mean average steady state concentration obtained was 35.0 ± 22.4 and 24.2 ± 10.1 mcg/mL, for responder (n=32) and non-responder (n=15), respectively. This suggests that a certain exposure may be required to obtain a response to treatment. The mean exposure obtained in the responders was about 59 % greater than what was achieved in the children with body weights < 20 kg suggesting that the doses administered to the patients who weighed < 20 kg may have resulted in less efficacious plasma concentrations despite the reduced apparent oral clearance. In addition, the medical reviewer (Dr. C. Yancey) informed this reviewer that the response rate to leflunomide in children who weighed < 40 kg was less (59% response rate) than those who weighed > 40 kg (80 % response rate). The doses administered to the patients who weighed < 40 and <20 kg was ½ and ¼ that of the adult dose, respectively. Since the CL in the patients who weighed < 20 kg was decreased by about one-third, the ¼ dose was probably too low for a response to treatment in spite of the reduced clearance.

Dosing Recommendation

Although the doses used in the pivotal efficacy and safety study (# 3503) were based on the pharmacokinetic data obtained from the pilot study (# 1037), the exposure and response data suggests that the doses administered to the children who weighed < 20 kg may have been sub-optimal, in spite of their reduced clearance. The sub-optimal doses predicted based on the model obtained in study # 1037 were probably because the relationship between CL and body weight was overestimated, so that the changes in CL with body weight was actually less than what was predicted. Thus, the reduction in doses predicted based on a linear relationship between CL and body weight was lower.

A refined leflunomide treatment regimen was proposed by the applicant to optimally target the desired median steady-state M1 concentration in the pediatric JRA population, considering the wide inter-subject variability and the formulation strengths available:

Body Weight (kg)	**Daily Dose** (mg)
10.0 – 19.9	10
20.0 – 40.0	15[a]
> 40.0	20

[a]To be administered as doses of 20 mg and 10 mg on alternating days

The table above shows that the proposed dose is ~ 100 % and 50 % higher than the studied doses for the patients with body weights < 20 kg and between 20-40 kg, respectively. Although the exposure data supports the increased dose, the limited safety data (confirmed with the medical reviewer, Dr. C. Yancey) in the pediatric population do not support the inclusion of these increased doses in the label.

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

/s/

Abi Adebowale
3/10/04 04:30:35 PM

Dennis Bashaw
3/10/04 04:41:08 PM