

# CLINICAL REVIEW

## Executive Summary Section

### Clinical Review for NDA 20-905

#### EXECUTIVE SUMMARY

The Food and Drug Administration (FDA) issued a Written Request (WR) on March 30, 1999, pursuant to Section 505A of the Federal Food, Drug and Cosmetic Act, to Aventis Pharmaceuticals, Inc. (Aventis) to obtain needed pediatric information on ARAVA (Leflunomide) tablets for the treatment of juvenile rheumatoid arthritis (JRA). Aventis responded to the Pediatric Written Request with Supplement-012 to NDA 20-905 consisting of the three studies.

#### I. RECOMMENDATIONS

##### A. RECOMMENDATION ON APPROVABILITY

This reviewer recommends approving NDA 20-905, Supplement-012 for labeling changes the Division has agreed to with the sponsor. The outcome of these trials does not support a pediatric indication but do provide useful clinical information about Arava (Leflunomide) in pediatric patients with polyarticular course JRA.

The Division recommends label changes in the following sections of the current approved Arava (Leflunomide) label: CLINICAL PHARMACOLOGY: Special Populations – Gender, Age and Pediatrics; CLINICAL STUDIES, Clinical Trials in Pediatrics, Reduction of signs and symptoms in pediatric patients with polyarticular course JRA.; PRECAUTIONS, Pediatric Use and ADVERSE REACTIONS, Pediatrics.

See Appendix IX., The Division's Proposed Label Changes for Arava (Leflunomide)

##### B. RECOMMENDATION ON PHASE 4 STUDIES AND/OR RISK MANAGEMENT STEPS

The Division recommends additional Phase IV studies with leflunomide, designed to include an active comparator, to better understand and determine the most appropriate leflunomide dose regimen in younger and older pediatric patients and further analyze the safety profile, efficacy outcomes and long-term tolerability of leflunomide in the treatment of pediatric patients with polyarticular course JRA.

#### II. SUMMARY OF CLINICAL FINDINGS

##### A. BRIEF OVERVIEW OF CLINICAL PROGRAM

1. Product Name: ARAVA<sup>7</sup> (Leflunomide) is a pyrimidine synthesis inhibitor, available for

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oral administration as 10, 20 or 100 mg tablets.

#### 2. Number of trials:

Study HWA486/1037, “Leflunomide in Pediatric Subjects with Polyarticular Course Juvenile Rheumatoid Arthritis”, was designed to collect pharmacokinetic and safety data from which to determine whether therapy with leflunomide warrants further study in patients with polyarticular course JRA, the JRA subtype which most closely resembles adult RA.

Study HWA486/3503, “Efficacy and Safety of Leflunomide versus Methotrexate in the Treatment of Pediatric Patients with Juvenile Rheumatoid Arthritis” was a randomized, double-blind, active-controlled study. This design was used because of the ethical considerations of with-holding treatment for a progressive disease with risk of irreversible disability for which approved therapeutic drugs exist.

Extension Study HWA486/3504, “Double-Blind, 8-Month Extension of Study HWA 486/3503 to Collect Durability of Efficacy Data and Additional Safety Data in Subjects with Juvenile Rheumatoid Arthritis Completing the Double-Blind Comparison Study, HWA486/3503, of Leflunomide versus Methotrexate”, was conducted over an eight month period to determine the durability of leflunomide versus the active comparator, methotrexate.

#### 3. Number of patients enrolled:

Study HWA486/1037	Enrolled 27 patients, 17 patients completed trial.
Study HWA486/3503	Enrolled 94 patients (screened 103 patients), 86 patients completed trial.
Study HWA486/3504	Enrolled 70 patients, trial is ongoing.

#### 4. Indications studied according to the pediatric written request: Signs and symptoms of Juvenile Rheumatoid Arthritis

#### 5. Overall number of patients exposed:

Study HWA486/1037	Enrolled 27 patients; exposed 27 to leflunomide; 17 patients completed 26 week protocol. (Enrolled patients had previously failed or were intolerant of methotrexate therapy.)
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Study HWA486/3503	Screened 103 patients; enrolled, randomized and exposed 94 patients; 47/94 patients exposed to leflunomide; 47/94 patients exposed to methotrexate; 42 completed leflunomide therapy; 44 completed methotrexate therapy. (Enrolled
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patients were naïve to treatment with either leflunomide or methotrexate.)

Study HWA486/3504      Exposed 33 patients to leflunomide and 37 patients to methotrexate; interim data summary (IDS) completed through week 8 (June 30, 2003); 22 exposed to leflunomide; 27 exposed to methotrexate.

The Division recommends additional investigation of leflunomide with larger Phase IV clinical trials to better understand the pharmacokinetic profile, safety and efficacy outcomes, the range of dosing, adverse event profile and long-term durability and tolerability in pediatric patients with signs and symptoms of polyarticular course JRA.

#### *B. EFFICACY*

Arava (Leflunomide) did not perform as well as the active comparator, methotrexate, using one of the co-primary efficacy endpoints, Juvenile Rheumatoid Arthritis Definition of Improvement  $\geq 30\%$  (JRA DOI  $\geq 30\%$ ), in the efficacy study submitted. The JRA DOI  $\geq 30\%$  responder rate in the active comparator group was 89.4% versus 68.1% in the leflunomide group. Leflunomide did not perform statistically better than the active comparator using the adjusted mean improvement analysis, -52.87% versus -44.41%, methotrexate versus leflunomide, respectively. Even though data did not support superiority of Leflunomide over the active comparator, the 68% responder rate for the JRA DOI is comparable to results in adult clinical trials.

The difference in efficacy favoring the active comparator, methotrexate, was particularly strong from the smaller and younger patients who were especially responsive to the relatively high methotrexate dose used in the efficacy study. The dose used for methotrexate was 0.5 mg/kg/week, (15 mg/m<sup>2</sup>/week), according to body weight in Study HWA486/3503 and Study HWA486/3504. The maximum allowable dose of methotrexate was 25 mg per week in both studies. The methotrexate dose described in the approved package insert explains that the recommended starting dose is 10 mg/m<sup>2</sup>/week.

The smaller and younger patients were less responsive to selected doses of Leflunomide. It appears that the smaller patients  $\leq 40$  kg were under-dosed compared to the patients  $> 40$  kg on the basis of 1) the M1 concentration being lower in the patients  $\leq 40$  kg, 2) efficacy was less in patients who were treated with the lower leflunomide doses and 3) adverse events were less frequent in patients  $< 40$  kg.

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Dosing was based on the initial PK Study HWA 486/1037 and assigned the adult loading and maintenance dose of one tablet (100 mg) per day x 3 consecutive days followed by 20 mg (two 10 mg tablets) for 16 weeks to patients > 40; for patients weighing 20 - 40 kg assigned one tablet (100 mg) per day for 2 consecutive days followed by 10 mg (one 10 mg tablet daily) for 16 weeks; and for patients weighing < 20 kg, assigned one tablet (100 mg) on one day followed by an average of 5 mg (one 10 mg tablet, every-other-day) for 16 weeks. However, the Population Pharmacokinetics (PPK) analysis that included data from Study HWA486/1037 and Study HWA486/3503 subsequently revealed that clearance in patients  $\leq$  40 kg is only reduced by a third compared to the adult dose.

The following summarizes results from the three studies submitted to support the requested label changes for Arava (Leflunomide):

#### Study HWA 486/1037

After 26 weeks of open-label study drug, leflunomide, administration, 51.9 % (14/27) of subjects were JRA DOI  $\geq$  30 % responders. Most of these subjects, 12 of 27 or 44.4 % of the total population achieved JRA DOI  $\geq$  50 % responses. Five of 27 subjects, 18.5 % attained a JRA DOI  $\geq$  70 % response. The body surface area (BSA)-rule for dosing leflunomide defined in the open-label study protocol was simplified in the subsequent double-blind protocol to dose adjustment based on body weight rather than BSA.

#### Study HWA 486/3503

Two co-primary endpoints were utilized in Study HWA486/3504 - the JRA DOI  $\geq$  30 % and the Percent Improvement Index.

Definitions of the two co-primary endpoints:

- **JRA DOI  $\geq$  30%** responder rate – is defined according to the patient's evaluation on 6 core set variables. Patients are classified as improved if they experienced  $\geq$  30 % improvement in at least three of the 6 core set variables, with no more than one of the 6 variables worsening by more than 30 %. The six variables used to calculate the 30 % improvement are: 1) disease severity, 2) overall well-being, 3) functional ability by the Childhood Health Assessment Questionnaire (CHAQ), 4) number of joints with active arthritis as defined by the ACR criteria, 5) number of joints with limited range of motion and the 6) erythrocyte sedimentation rate (ESR).
- **Percent Improvement Index** – is defined as the mean of the percent changes from baseline for all 6 DOI core set variables. This value is calculated for each subject as follows: (current value - baseline value) / baseline value x 100. Note: if the current value was negative, worse than

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baseline, the value was set to zero. The PPI is a continuous variable in which the JRA trial experience is limited. (The Division did not find the Percent Improvement Index sufficient as a single efficacy endpoint; hence, two co-primary endpoints in Study HWA486/3503 and Extension Study HWA486/3504.)

There was no statistically significant difference between leflunomide versus methotrexate treated polyarticular course JRA treatment groups in Percent Improvement Index at Week 16. The adjusted mean improvement was - 44.41 % and - 52.87 % for leflunomide versus methotrexate, respectively. Note: the larger the negative value, the more improved the clinical response. However, methotrexate performed statistically better than leflunomide, as measured by the JRA DOI  $\geq 30$  % responder rate. The JRA DOI  $\geq 30$  % responder rate was 89.4 % versus 68.1 %, methotrexate versus leflunomide, respectively. JRA DOI  $\geq 50$  % and  $\geq 70$  % responder rates were analyzed as secondary outcome variables and did not demonstrate statistically significant differences between the treatment groups at Week 16.

Extension Study HWA486/3504 collected ongoing blinded data from Week 16 through Week 24. There were no substantive changes in outcome measures; efficacy results were maintained through this 8 week period.

#### C. SAFETY

Safety information was collected from a total of 73 pediatric patients (27 patients from Study HWA486/1037 and 47 patients from Study HWA486/3503) who were treated with leflunomide. There were no deaths, malignancies, significant overdoses or pregnancies in these three clinical trials. There were a total of 21 serious adverse events across all three clinical trials. The overall safety profile of adverse events was consistent with the underlying disease and the known adverse events of leflunomide. The most common adverse events included abdominal pain, diarrhea, nausea, vomiting, oral ulcers, upper respiratory tract infections, alopecia, rash, headache and dizziness. Less commonly seen adverse events included anemia, hypertension and weight loss. Hepatotoxicity is a well know risk factor of leflunomide treatment. There were 14 of 74 patients who experienced elevated ALT or AST elevations.

#### D. DOSING

No dosing regimen for pediatric patients with polyarticular course JRA can be recommended on the basis of the findings in NDA 20-905, Supplement-012. The dosing utilized during study HWA486/3503 was not associated with a finding of efficacy when compared with the results from methotrexate-treated patients. The dosing used for patients  $> 40$  kg body weight was comparable to adult dosing of leflunomide based on PK data. In Study HWA486/3503 and Study HWA486/3504, leflunomide dosage was

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administered to pediatric patients based on body weight rather than body surface area, which was initially utilized in Study HWA486/1037.

**Table 1.** Leflunomide pediatric dose calculations for clinical efficacy Study HWA486/3503 and Study HWA486/3504. (The following table is from the sponsor's submission)

Patient Weight (kg)	Loading dose	Loading dose mg/day	Maintenance dose mg/day
< 20 kg	1 x 100 mg	1 tablet (100 mg) on one day	Average of 5 mg (one 10 mg tablet QOD) for 16 weeks
20 – 40 kg	2 x 100 mg	1 tablet (100 mg) per day for 2 consecutive days	10 mg (one 10 mg tablet daily) for 16 weeks
> 40 kg	3 x 100 mg	1 tablet (100 mg) per day for 3 consecutive days	20 mg (two 10 mg tablets daily) for 16 weeks

As noted in **Table 1**, smallest and youngest patients received a loading dose that was approximately 25% less than the adult daily dosing. To efficiently prescribe available manufactured tablet forms of Arava, the sponsor selected an alternate day dosing schedule for the very smallest and youngest patients (20 kg body weight) treated in the leflunomide group.

#### E. Special Populations

Juvenile Rheumatoid Arthritis (JRA) is one of the most common rheumatic diseases of childhood. The incidence of JRA varies from 2 to 22 per 100,000 population.<sup>1,2,3</sup> The American College of Rheumatology (ACR) criteria defines JRA as having three subtypes: pauci-articular, polyarticular and systemic type JRA.

Study HWA486/1037, Study HWA486/3503 and Study HWA486/3504 selected polyarticular course JRA for investigation of the Disease Modifying Anti-Rheumatic Drug (DMARD), Arava (Leflunomide). The reviewer notes that polyarticular course JRA reflects the JRA subtype most likely to be exposed to DMARD therapy and that most closely resembles adult rheumatoid arthritis, especially rheumatoid factor positive polyarticular JRA. The reviewer also concurs that individuals with systemic JRA are at greater risk for hepatotoxicity and/or hematologic sequelae, specifically, disseminated intravascular coagulation (DIC), and were, therefore, not included in these trials.

#### References

1. Laaksonen AL: *A prognostic study of juvenile rheumatoid arthritis. Analysis of 544 Cases. Acta Paediatr Scand Suppl 1996, pp 1-163.*
2. Oen KG, Cheang M: *Epidemiology of chronic arthritis in childhood. Semin Arthritis Rheum 26: 575-591, 1996.*

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3. *Gare BA: Juvenile Chronic Arthritis. A Population Based Study on Epidemiology, Natural History and Outcome. Goteborg Sweden, University of Goteborg, 1994.*

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