



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research**

**Memorandum**

DATE: March 29, 2005

FROM: Renan A. Bonnel, Pharm.D., MPH  
Postmarketing Safety Evaluator  
Division of Drug Risk Evaluation, HFD-430  
Office of Drug Safety

THROUGH: Mark Avigan, M.D., C.M., Director  
Division of Drug Risk Evaluation, HFD-430  
Office of Drug Safety

TO: Solomon Iyasu, M.D., M.P.H., Team Leader  
Division of Pediatric Drugs and Development, HFD-960

SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event  
Review (PID #: D030661)  
Leflunomide (Arava®), NDA 20-905  
Pediatric Exclusivity Approval Date: November 10, 2003

**Note: This document replaced the document DFS'ed on January 14, 2005**

**Executive Summary**

As requested by the Office of Counter-Terrorism and Pediatrics (OCTAP), we reviewed the pediatric adverse events in association with the use of leflunomide (Arava®) in children aged 16 years and younger. The time period of interest was the one-year period following the FDA Pediatric Exclusivity approval, from November 10, 2003 through December 10, 2004. The date of December 10, 2004 was selected as the data termination date to allow for one-month lag time for report entry into AERS.

There were two foreign reports of hepatotoxicity associated with leflunomide in this time period. One was a study report of elevated aminotransferases in a 12 year old male. The child received the study medication (leflunomide) and developed elevated alanine aminotransferase after 6 months of therapy. The study medication was discontinued and the child recovered without sequelae. An elevated alanine aminotransferase is a labeled event for adult patients in the labeling.

The second case involved a 14 year old female who took an overdose of acetaminophen (over 20 tablets) while receiving leflunomide 20 mg daily. She presented with mild

disorientation, vomiting and developed acute liver failure. The patient received cholestyramine, unspecified treatment for acetaminophen overdose and fully recovered. This appears to be a case of acetaminophen overdose.

Current leflunomide product labeling does provide safety data from the clinical studies. We will continue monitoring reports of adverse events in pediatric patients receiving leflunomide to increase our understanding of leflunomide's effects in children.

### **AERS Search Results**

AERS Search Date: Searches for U.S./foreign cases during the following time periods, (1) September 10, 1998 (approval date) to December 10, 2004, and (2) November 10, 2003 (pediatric exclusivity date) to December 10, 2004.

#### **A. Adverse events from marketing approval date, September 10, 1998 to December 10, 2004:**

##### **1. Raw counts of reports**

	All reports (US)	Serious (US)	Deaths (US)
All ages	3620* (1804)	3061 (1275)	368 (156)
Adults (≥ 17 yrs)	2922 (1298)	2571 (972)	322 (127)
Peds (0-16 yrs)	26 (17)	24 (15)	2 (0)

\* includes 281 null age values

##### **2. Top 20 reported adverse event PT's and labeling status of these events (underlined denotes unlabeled events):**

###### *All ages:*

Diarrhea (322), alanine aminotranferase increased (240), aspartate aminotranferase increased (234), pyrexia (222), nausea (191), liver function test abnormal (190), blood alkaline phosphatase increased (178), dyspnea (169), asthenia (168), weight decreased (153), vomiting (148), hemoglobin decreased (139), condition aggravated (137), sepsis (133), anemia (127), pneumonia (127), gamma glutamyltransferase increased (122), pancytopenia (122), hypertension (116), headache (114)

###### *Adults:*

Diarrhea (300), alanine aminotranferase increased (224), aspartate aminotranferase increased (221), pyrexia (209), nausea (180), blood alkaline phosphatase increased (169), liver function test abnormal (162), asthenia (161), dyspnea (156), vomiting (141), weight decreased (140), condition aggravated (131), hemoglobin decreased (129), sepsis (120), gamma glutamyltransferase increased (116), anemia (115), pancytopenia (110), headache (109), pneumonia (106), hypertension (105)

*Pediatrics:*

Maternal drugs affecting foetus (10), complications of maternal exposure to therapeutic drugs (8), premature baby (7), pregnancy (4), arthralgia (3), caesarean section (3), neonatal disorder (3), neonatal respiratory distress syndrome (3), cardiac murmur (2), cyst (2), dermatitis (2), drug exposure during pregnancy (2), liver function test abnormal (2), premature rupture of membranes(2), respiratory distress (2), scratch (2), small for dates baby (2), twin pregnancy (2), vomiting (2), alanine aminotransferase increased (1).

**B. From Pediatric Exclusivity approval date (November 10, 2003) through AERS data cut-off date December 10, 2004:**

**1. Raw counts of reports**

	All reports (US)	Serious (US)	Deaths (US)
All ages	685* (196)	668 (190)	174 (61)
Adults (≥ 17 yrs)	609 (161)	593 (156)	96 (52)
Peds (0-16 yrs)	2 (0)	2 (0)	0 (0)

\* includes 74 null age values

**2. Top 20 reported adverse event PT's and labeling status of these events (underlined denotes unlabeled events):**

*All ages:*

Alanine aminotranferase increased (144), aspartate aminotranferase increased (137), blood alkaline phosphatase increased (104), diarrhea (79), gamma glutamyltransferase increased ( 74), blood lactate dehydrogenase increased (71), pyrexia (41), nausea (56), hemoglobin decreased (49), pancytopenia (44), vomiting (41), anaemia (40), dyspnea (40) , interstitial lung disease (39), asthenia (37), abdominal pain (36) , white blood cell count increased (35), blood bilirubin increased (33), liver function test abnormal (33), platelet count decreased (32)

*Adults:*

Alanine aminotranferase increased (135), aspartate aminotranferase increased (132), blood alkaline phosphatase increased (99), diarrhea (78), gamma glutamyltransferase increased (72), blood lactate dehydrogenase increased (71), pyrexia (57), nausea (55), hemoglobin decreased (45), pancytopenia (44), anemia (39), interstitial lung disease (39), vomiting (39), dyspnea (38), abdominal pain (36), asthenia (35), white blood cell count increased (34), blood bilirubin increased (32), platelet count decreased (32), rash (31)

*Pediatrics:*

Alanine aminotransferase increased (1), ammonia increased (1), blood potassium decreased (1), blood sodium increased (1), coagulation factor V level decreased (1), coagulation factor VII level decreased (1), disorientation (1), hematocrit decreased (1), **hepatic failure (1)**, hepatotoxicity (1), international normalized ratio increased (1), overdose (1), oxygen saturation decreased (1), Pco<sub>2</sub> increased (1), platelet count increased (1), Po<sub>2</sub> increased (1), prothrombin time prolonged (1), vomiting (1), white blood cell count increased (1).

**Postmarketing Review of All Peds Adverse Event Reports from November 10, 2003 to December 10, 2004**

There were two foreign reports in this time period.

**A. Narratives of the pediatric cases.**

The first case was a study report (ISR# 4304561) of elevated aminotransferases in a 12 year old male. The child received the study medication (leflunomide) and developed elevated alanine aminotransferase (192 U/L and 127 U/L ; reference range: 6-43 U/L) after 6 months of therapy. The dosing information was not provided. The study medication was discontinued and the child recovered without sequelae. The concomitant medications included indomethacin, omeprazole, metoclopramide, and folic acid. The reporter considered the adverse event related to leflunomide.

The second report (ISR # 4441603) involved a 14 year old female who took an overdose of acetaminophen (over 20 tablets) while receiving leflunomide 20 mg daily. She was an adult size adolescent and was given an adult dose. She presented with mild disorientation, vomiting and developed an acute liver failure. The concomitant medications included prednisone, naprosyn, and ranitidine.

The abnormal laboratory values included: ALT (highest 8351 U/L), AST (highest 9757 U/L), ammonia (highest 93 µmol/L), GGT (238, ref: 0-45 U/L), bilirubin (highest 24 µmol/L, ref 0-17), conjugated bilirubin (highest 48, ref 0-2 mol/L), hypokalemia (lowest 3.2 mmol/L, ref: 3.7-5), INR (6 units, ref: 0.9-1.1), PTT (43 sec, ref: 25-35), Factor V (0.03 IU/ml, ref: 0.70- 1.34), increased platelet count (453 x 10<sup>9</sup>/L) , WBC (23.6 units, ref 4-10). She received cholestyramine 8 grams three times daily for elimination of leflunomide and unspecified therapy for acetaminophen overdose. The patient fully recovered.

**B. Comments regarding pediatric studies, labeling status of the top 20 adverse events.**

In March 1999, the FDA issued a written request to study Arava in the pediatric population with polyarticular juvenile rheumatoid arthritis (JRA). The reports for the clinical trial were submitted on 9/4/2003 and the pediatric exclusivity was granted on

11/10 /2003. Susan McCune, M.D. (CDER, OCTAP) reviewed the pediatric studies and proposed label changes on 2/27/2004 in a memorandum to DAAODP <sup>1,2</sup>.

The following paragraphs are the excerpts from her review. “There were three studies that were performed with leflunomide in population, 3 to 17 years of age (at least one third less than or equal to 12 years of age) who had a clinical diagnosis of polyarticular JRA. The first study was an open label study enrolling patients who had previously failed treatment or were intolerant of MTX therapy. Study 2 was the pivotal study which was randomized, double-blind parallel group 16 week treatment comparing Arava to MTX. Study 3 was an extension study for 8 months to follow safety, tolerability and durability of the efficacy of Arava versus MTX ”.

“Adverse reactions associated with use of leflunomide in pediatric patients with polyarticular course juvenile rheumatoid arthritis were most commonly abdominal pain, diarrhea, nausea or vomiting, respiratory infections as nasopharyngitis or pharyngitis, oral ulcers, weight loss, alopecia, headache, and dizziness. In one clinical trial, four of 47 subjects receiving ARAVA had ALT elevations > 1.2 x ULN and < 2 x ULN”.

“Safety information was collected from a total of 73 pediatric patients (Study 1 and Study 2) who were treated with leflunomide. There were no deaths, malignancies, significant overdoses or pregnancies in these three 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 and the known adverse effects of leflunomide. The most common adverse events included abdominal pain, diarrhea, nausea or vomiting, respiratory infections as nasopharyngitis or pharyngitis, oral ulcers, weight loss, oral ulcers, weight loss, alopecia, headache, and dizziness. In one clinical trial, four of 47 subjects receiving ARAVA had ALT elevations > 1.2 x ULN and < 2 x ULN”

On 2/27/2004, Dr. McCune recommended to separately label adverse event information for pediatric and adult patients<sup>1</sup>. The current labeling approved on 11/22/2004 includes abdominal pain, diarrhea, nausea, vomiting, oral ulcers, upper respiratory tract infections, alopecia, rash, headache, dizziness, anemia, hypertension, weight loss and elevated ALT and /or AST under a separate adverse reactions section for pediatric population.

AERS cases: In our review of pediatric leflunomide cases, only one report of liver failure was identified, and this event was more closely associated with acetaminophen toxicity. This information is insufficient to draw a conclusion regarding the frequency of liver failure with leflunomide use in children.

### **Conclusion**

There were two reports of hepatotoxicity associated with leflunomide (Arava®) for the 12-month time period after pediatric exclusivity was granted. One report was from a

foreign study report and the patient received leflunomide (unknown dose) and developed elevated aminotransferases. This is a labeled adverse event and the reporter considered the adverse event related to leflunomide. The second child (reported to be an adult size adolescent) developed liver failure after receiving large amounts of acetaminophen and 20 mg of leflunomide (recommended adult dose). Both patients recovered.

Current leflunomide product labeling does provide safety data from the pediatric clinical studies. We will continue monitoring reports of adverse events in pediatric patients receiving leflunomide to increase our understanding of leflunomide's effects in children.

REFERENCES:

1. Susan McCune, MD. - Arava (leflunomide) Efficacy Supplement Label Consult (NDA # 20-905) , DFS date: March 3, 2004.
2. Carolyn Yancey, MD. - Pediatric Clinical Review for NDA# 20-905.  
[http://www.fda.gov/cder/foi/esum/2004/20905se5012\\_Arava\\_Clinical\\_BPCA.pdf](http://www.fda.gov/cder/foi/esum/2004/20905se5012_Arava_Clinical_BPCA.pdf)

---

Renan A. Bonnel, Pharm.D., MPH  
Safety Evaluator, Division of Drug Risk Evaluation

Concur;

---

Lauren Lee, Pharm.D.  
Acting Team Leader, Division of Drug Risk Evaluation

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

/s/

-----  
Renan Bonnel  
3/29/05 02:01:59 PM  
DRUG SAFETY OFFICE REVIEWER

Mark Avigan  
3/29/05 03:03:33 PM  
DRUG SAFETY OFFICE REVIEWER