Aventis Pharmaceuticals

October 2003

IMPORTANT PRESCRIBING INFORMATION

Dear Healthcare Professional:

Aventis Pharmaceuticals wants to keep you informed of important updates to the safety information for Arava® (leflunomide) tablets. Arava® is indicated in adults for the treatment of active rheumatoid arthritis (RA) to reduce signs and symptoms, inhibit structural damage as evidenced by x-ray erosions and joint space narrowing, and, now, also, to improve physical function, an expanded indication recently approved by the FDA.

In postmarketing experience worldwide, rare, serious, hepatic injury, including cases with fatal outcome, have been reported during treatment with Arava®. Most cases occur within 6 months of therapy and in a setting of multiple risk factors for hepatotoxicity. It should be emphasized that multiple confounding factors were present in most of the cases, such as preexisting hepatic disease, comorbid illness predisposing to hepatic complications, and concomitant potentially hepatotoxic medications.

Rare postmarketing reports of severe infections including sepsis, which may be fatal, have also been received. 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.

As part of postmarketing pharmacovigilance, Aventis Pharmaceuticals has updated the prescribing information and monitoring recommendations to include these rare, serious adverse events.

The **WARNINGS** - **Hepatotoxicity** section of the prescribing information provides further guidance regarding duration of the initial monthly liver enzyme monitoring, intervals for monitoring in the maintenance of treatment, and dose discontinuation for confirmed ALT elevations more than 3 times the upper limit of normal (ULN). The following revised paragraphs are shown:

> **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).

Aventis Pharmaceuticals · 300 Somerset Corporate Boulevard · Bridgewater, NJ 08807-2854
Telephone (908) 243-6000 · www.aventis.com

At minimum, ALT (SGPT) must be performed at baseline and monitored initially at monthly intervals during the first 6 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 10mg/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 a 6-month study of 263 patients with persistent active RA 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 3 times the ULN was observed in 3.8% of patients compared with 0.8% in 130 patients continued on methotrexate with placebo added.

The **WARNINGS – Immunosuppression Potential/Bone Marrow Suppression** section has additional narrative, as shown below, to emphasize that interruption of therapy with Arava® may be necessary if a serious infection occurs while on Arava®. This follows the previous warning that 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 immunosuppresion 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 6 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).

The **PRECAUTIONS - Laboratory Tests** section has been updated with the same monitoring information updated in the **WARNINGS - Hepatotoxicity** section and in the **Immunosuppression Potential/Bone Marrow Suppression** section as discussed above.

The **ADVERSE REACTIONS** section has also been modified to reflect these safety updates.

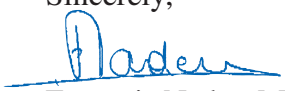
The **CLINICAL STUDIES** section has been updated to include information on physical function and maintenance of effect.

We hope this information will be helpful to you in caring for your patients with RA. From September 1998, when Arava® was approved in the US, through September 2002, approximately 580,000 patients have been treated with Arava® worldwide.[1] The overall safety profile and postmarketing experience with Arava® otherwise remain consistent with the safety and efficacy demonstrated in our extensive clinical-trial program.

Please see the enclosed prescribing information. For more information about the revised prescribing information, please contact Aventis Pharmaceuticals Medical Information Services at (800) 633-1610.

We rely on detailed medical feedback from prescribers to effectively delineate the issues described above and update the general safety profile of our products. You can assist in monitoring the safety of Arava® by reporting all adverse events to the Aventis Pharmaceuticals Medical Information Services at (800) 633-1610; or to the FDA MEDWATCH program: by phone at (800) FDA-1088; by fax at (800) FDA-0178; via the MEDWATCH Web site at www.fda.gov/medwatch; or by mail (using postage-paid form) at: MEDWATCH, HF-2 5600 Fishers Lane, Rockville, MD 20857-9787.

Sincerely,



Francois Nader, MD, MBA
Senior Vice President, Medical Affairs North America
Aventis Pharmaceuticals

1. Data on file. Aventis Pharmaceuticals.

ARA-LT-10773-1