**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

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

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/s/

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Lee Simon

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