DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-905/S-014

Aventis Pharmaceuticals, Inc.
Attention: Jay Kraker
Associate Specialist, Regulatory Affairs
200 Crossing Boulevard, Mailstop: BX2-309E
Bridgewater, NJ 08807-0890

Dear Mr. Kraker:

Please refer to your supplemental new drug application dated May 26, 2004, received May 27, 2004, 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 dated May 26 and August 16, 2004.

This supplemental new drug application provides for labeling changes that incorporate all changes from the approved S-006, S-007 and S-012 supplements as well as a change of product labeling to 1) provide geriatric use information and 2) update the **ADVERSE REACTIONS** section and **PRECAUTIONS** section regarding post-marketing reports of interstitial lung disease.

We completed our review of this application,as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below and indicated in the enclosed labeling:

1. Line 1: changes the month of revision
2. Line 399: corrects reference to table number
3. Line 475: adds a paragraph on Interstitial Lung Disease to **PRECAUTIONS** section
4. Line 604: adds a paragraph on Geriatric Use to **PRECAUTIONS** section
5. Line 671: adds language to **ADVERSE REACTIONS** post marketing section for Respiratory
6. Line 741: changes the month of revision
7. Line 744: name change of the manufacturer
8. Line 751: changes the copyright year

The Division recommends the following language in item 3 in lieu of your wording (see line 475):

> "Interstitial lung disease has been reported during treatment with leflunomide and has been associated with fatal outcomes (**see ADVERSE REACTIONS).** Interstitial lung disease is a potentially fatal disorder, which may occur acutely at any time during therapy and has a variable clinical presentation. New onset or worsening pulmonary symptoms, such as cough and dyspnea, with or without associated fever, may be a

reason for discontinuation of the therapy and for further investigation, as appropriate. If discontinuation of the drug is necessary, initiation of wash-out procedures should be considered. (see **WARNINGS – Drug Elimination Procedure).**"

The Division recommends the following change in item 4 to formatting under **PRECAUTIONS – Information for Patients** (see line 492):

Place bullets in front of lines 493, 500, 503, and 506 sentences.

Add the bullet at line 513: "Patients should be informed about the early warning signs of interstitial lung disease and asked to contact their physician as soon as possible if these symptoms appear or worsen during therapy."

In item 5, the Division recommends adding the following under **ADVERSE REACTIONS** at line 671 after "interstitial lung disease":

"including interstitial pneumonitis and pulmonary fibrosis, which may be fatal;"

The following punctuation and formatting changes are suggested by the Division and identified by line number:

9. Throughout the label, parenthetical references to other sections of the label are inserted. However, the formatting is not consistent. The Division suggests that all parenthetical references to other sections be consistent throughout the label.
10. Formatting changes were made to the major subject headings, minor subject headings and subsection headings so as to be consistent throughout the label. Underlining was removed and words were italicized where appropriate (see attached label).
11. The entire **Drug Interactions** section of the **PRECAUTIONS** section was moved to precede the **Carcinogenesis, Mutagenesis, and Impairment of Fertility** section so as to comply with 21 CFR 201.57.
12. Line 126: added a semi-colon after "unknown".
13. Line 132: bolded parenthetical reference
14. Line 178: added a comma after "total".
15. Line 181: capitalized the T in "table".
16. Line 198: capitalized the T in "table".
17. Line 213: capitalized the T in "table".
18. Line 245: added a comma after "addition".
19. Line 297: capitalized "Pediatrics" heading.
20. Line 309: changed Pharmacokinetics to lower case and bold
21. Line 317: bolded parenthetical reference.
22. Line 320: bolded parenthetical reference, removed underline, italicized last word
23. Line 322: bolded parenthetical reference, removed underline.
24. Line 353: bolded parenthetical reference.
25. Line 370: bolded parenthetical reference, removed underline.
26. Line 392: bolded parenthetical reference, removed underline.
27. Line 415: capitalized Warnings, bolded parenthetical reference, removed underline.
28. Line 421: bolded parenthetical reference, removed underline.
29. Line 432: bolded parenthetical reference.

30. Line 477: bolded parenthetical reference.
31. Line 498: bolded parenthetical reference, removed underline.
32. Line 522: removed the extra word "with".
33. Line 523: bolded parenthetical reference, removed underline.
34. Line 530: bolded parenthetical reference.
35. Line 538: bolded parenthetical reference, removed underline.
36. Line 548: bolded parenthetical reference.
37. Line 552: added a semi-colon after "unknown".
38. Line 579: added a space between "HGPRT" and "Gene".
39. Line 586: added parentheses and bolded parenthetical reference.
40. Line 602: bolded parenthetical reference.
41. Line 605: added a comma after ARAVA.
42. Line 625: added a comma after "leflunomide".
43. Line 673: added a semi-colon after "neuropathy".
44. Line 699: bolded parenthetical reference.
45. Line 703: bolded parenthetical reference, removed underline.
46. Line 706: bolded parenthetical reference, removed underline.
47. Line 718: bolded parenthetical reference, removed underline.
48. Line 725: bolded parenthetical reference, removed underline.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the enclosed labeling text for the package insert and text for the patient package insert. These revisions are terms of the approval of this application.

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 15 of the copies on heavy-weight paper or similar material. In addition, submit content of labeling in electronic format (.pdf and .doc) as required by 21 CFR 314.50(l)(5). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-905/S-014. Approval of this submission by FDA is not required before the labeling is used.

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 14.80 and 314.81).

If you have any questions, call Ms. Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Office of drug Evaluation V
Center for Drug Evaluation and Research

Enclosure:

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

/s/

Sharon Hertz

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