DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 14-214/S-057

sanofi-aventis U.S. LLC
Attention: Mr. Bradley Jones
RAC, Specialist, Heritage Product Support
U.S. Regulatory Affairs Marketed Products
55 Corporate Dr.
Bridgewater, NJ 08807

Dear Mr. Jones:

Please refer to your supplemental new drug application dated May 3, 2007, received May 4, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NegGram® (nalidixic acid, USP) Caplets, 500 mg.

This "Changes Being Effected" supplemental new drug application, submitted in response to the Supplement Request letter issued by the Division on October 30, 2006, provides for changes to the **WARNINGS** section and **PRECAUTIONS/ Information for Patients** subsection, as follows (additions are underline and deletions are ~~strikethrough~~):

1. The fourth, fifth and sixth paragraphs in the **WARNINGS** section (the paragraphs regarding pseudomembranous colitis and *C. difficile*) was replaced with the underlined text below.

   ~~Pseudomembranous colitis has been reported with nearly all antibacterial agents, including quinolones, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.~~

   ~~Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".~~

   ~~After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.~~

   Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including NegGram, and may range in severity from mild diarrhea to fatal

colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

2. Under the **PRECAUTIONS/Information for Patients** subsection, the following text was added after the last dash:

   - that diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

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 agreed upon during the May 17, 2007, teleconference between Kristen Miller, Pharm.D., and yourself listed below:

1. The microorganisms and term "*in vitro*" throughout the labeling have been italicized.

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
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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 Kristen Miller, Pharm.D., Regulatory Health Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
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/

Renata Albrecht

5/24/2007 01:49:39 PM