DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 14-214/S-059

SUPPLEMENT APPROVAL

Sanofi-aventis U.S. Inc.
Attention: Katherine Ng, Pharm.D.
Specialist, Base Business Product Support
U.S. Regulatory Affairs Marketed Products
55 Corporate Drive, P.O.Box 5925
Bridgewater, NJ 08807

Dear Dr. Ng:

Please refer to your supplemental new drug application (sNDA) dated and received February 17, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NegGram (nalidixic acid) Caplets, 500 mg.

We also acknowledge receipt of your amendment dated March 25, 2011.

This "Prior Approval" supplemental new drug application provides for the following revisions to the package insert (deletions are noted by ~~strikethrough~~ text and additions are noted by double underlined text).

1. The **MICROBIOLOGY** section of the package insert is revised as follows:

Mechanism of Action
Nalidixic acid blocks DNA replication in susceptible bacteria by inhibiting a subunit of DNA gyrase.
~~NegGram has marked antibacterial activity against gram-negative bacteria including *Enterobacter* species, *Escherichia coli*, *Morganella Morganii*; *Proteus Mirabilis*, *Proteus vulgaris*, and *Providencia rettgeri*. *Pseudomonas* species are generally resistant to the drug. NegGram is bactericidal and is effective over the entire urinary pH range.~~

Drug Resistance
Conventional chromosomal resistance to ~~NegGram~~ nalidixic acid taken in full dosage has been reported to emerge in approximately 2 to 14 percent of patients during treatment; however, bacterial resistance to NegGram has not been shown to be transferable via R factor.

Activity *in vitro* and *in vivo*

Nalidixic acid has marked antibacterial activity against gram-negative bacteria including *Enterobacter* species, *Escherichia coli*, *Morganella morganii*; *Proteus mirabilis*, *Proteus vulgaris*, and *Providencia rettgeri*. *Pseudomonas* species are generally resistant to the drug. Nalidixic acid is bactericidal and is effective over the entire urinary pH range.

Susceptibility Test

Diffusion Techniques

Quantitative methods that require measurement of zone diameters give the most precise estimates of antibacterial susceptibility. One such procedure recommended for use with a disc containing 30 mcg of nalidixic acid is the ~~National Committee for Clinical Laboratory Standards (NCCLS)~~ Clinical and Laboratory Standards Institute (CLSI) approved procedure[1]. Only organisms from urinary tract infections should be tested. Results of laboratory tests using 30 mcg nalidixic acid discs should be interpreted ~~using~~ according to the ~~following~~ criteria~~:~~ outlined in Table 1.

~~**Zone Diameter (mm) Interpretation**~~
~~≥19 (S) Susceptible~~
~~14-18 (I) Intermediate~~
~~≤13 (R) Resistant~~

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Broth and agar dilution methods, such as those recommended by the ~~NCCLS~~ CLSI[2], may be used to determine the minimum inhibitory concentration (MIC) of nalidixic acid. MIC test results should be interpreted according to the ~~following~~ criteria~~:~~ outlined in Table 1.

~~**MIC (mcg/mL) Interpretation**~~
~~≤16 (S) Susceptible~~
~~≥32 (R) Resistant~~

Table 1: Susceptibility Interpretive Criteria for nalidixic acid

MIC (μg/mL)			**Zone diameter (mm)**		
S	**I**	**R**	**S**	**I**	**R**
≤ 16	-	≥ 32	≥ 19	14-18	≤ 13
S=Susceptible, I=Intermediate, and R=Resistant					

~~For any susceptibility test, a report of "susceptible" indicates that the pathogen is likely to respond to nalidixic acid therapy. A report of "resistant" indicates that the pathogen is not likely to respond. A report of "intermediate" generally indicates that the test result is equivocal.~~

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if

the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

Quality Control

~~The Quality Control strains should have the following assigned daily ranges for nalidixic acid:~~

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. For dilution technique, standard nalidixic acid powder should provide the MIC values provided in Table 2. For diffusion technique, the 30-µg nalidixic acid disk should provide the zone diameters outlines in Table 2.

Table 2: Quality Control for Susceptibility Testing		
Strains	**MIC range (µg/mL)**	**Zone Diameter (mm)**
Escherichia coli ATCC 25922	1-4	22-28

~~**QC Strains**~~

~~E. Coli~~

~~(ATCC 25922)~~

~~**Disc Zone Diameter**~~

~~22-28~~

~~**MIC (mcg/mL)**~~

~~1.0-4.0~~

2. A new **REFERENCES** section is added as follows:

REFERENCES

1. Clinical and Laboratory Standards Institute, Performance standards for antimicrobial disk susceptibility tests - Tenth edition, Approved Standard CLSI Document M2-A10, Vol. 29, No. 1, CLSI, Villanova, PA, 2009.
2. Clinical and Laboratory Standards Institute, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically - Eight edition, Approved Standard CLSI Document M7-A8, Vol. 29, No. 2, NCCLS, CLSI, Villanova, PA, 2009.

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

a. In the **MICROBIOLOGY/Drug Resistance** subsection, in the last sentence, the word "NegGram" should be replaced with the words "nalidixic acid" as follows:

Drug Resistance
Conventional chromosomal resistance to nalidixic acid taken in full dosage has been reported to emerge in approximately 2 to 14 percent of patients during treatment; however, bacterial resistance to ~~NegGram~~ nalidixic acid has not been shown to be transferable via R factor.

b. In the **REFERENCES** section, at the end of both references, the word "Villanova" should be replaced with the word "Wayne:"

REFERENCES
1. Clinical and Laboratory Standards Institute, Performance standards for antimicrobial disk susceptibility tests - Tenth edition, Approved Standard CLSI Document M2-A10, Vol. 29, No. 1, CLSI, ~~Villanova~~ Wayne, PA, 2009.
2. Clinical and Laboratory Standards Institute, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically - Eight edition, Approved Standard CLSI Document M7-A8, Vol. 29, No. 2, NCCLS, CLSI, ~~Villanova~~ Wayne, PA, 2009.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to, except with the revisions listed above, the enclosed labeling (text for the package insert, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application and with the revisions listed above, as well as annual reportable

changes, and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

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, call Maureen Dillon Parker, Chief, Project Management Staff at (301) 796-1400.

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: Package Insert

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
04/29/2011