CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-430/S-026, S-027

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

NDA 14-214/S-050, S-051
NDA 17-430/S-026, S-027

Regulatory Review Officer's Review of Supplemental Labeling Revisions (SLR):

Materials Reviewed:
NDA 14-214

SLR	Date submitted	Date received	Date completed
050	December 4, 1998	December 7, 1998	November 1, 1999
051	April 27, 1999	April 30, 1999	November 1, 1999
Amendments:			
050, 051	May 21, 1999	May 24, 1999	November 1, 1999
050	October 26, 1999	November 1, 1999	November 1, 1999

NDA 17-430

SLR	Date submitted	Date received	Date completed
026	December 4, 1998	December 7, 1998	November 1, 1999
027	April 27, 1999	April 30, 1999	November 1, 1999
Amendments:			
026, 027	May 21, 1999	May 24, 1999	November 1, 1999
026	October 26, 1999	November 1, 1999	November 1, 1999

- FPL for NDAs 14-214/S-044 and 17-430/S-019 dated April, 1996
- Package insert for NDAs 14-214 and 17-430 dated May, 1998
- FDA letter to the company dated February 3, 1999 concerning quinolone labeling requirements
- Fax to company dated October 21, 1999 requesting revisions to the Geriatric Use section of the label

Sponsor: Sanofi-Synthelabo Inc.

Product: NegGram® (nalidixic acid caplets) Caplets, 250 mg, 500 mg, 1 g
NegGram® (nalidixic acid suspension) Suspension, 250 mg/5 mL

Background:
NDA 14-214 (NegGram® Caplets) was originally approved on March 6, 1964. NDA 17-430 (NegGram Suspension) was originally approved on April 17, 1973. These NDAs share a combined label. The latest labeling revision was approved on February 7, 1995 for NDA 14-214/S-044 and NDA 17-430/S-019. FPL for these supplements was dated April, 1996. There have been no approved labeling changes since that time.

NDA 14-214/S-050 and NDA 17-430/S-026 were submitted in response to the Federal Register notice dated August 27, 1997 that advised companies to revise geriatric labeling. On February 18, 1999, the Medical Officer, Dr. Marc Cavaille-Coll, completed his

review of these supplements and determined that the wording in the **PRECAUTIONS** section, **Geriatric Use** subsection needed to be revised to reflect the instructions in the Federal Register notice. The company's proposed wording was acceptable except for the following statement:

[ ]

Dr. Cavaille-Coll proposed that the statement above be deleted and replaced with:

> "This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See **PRECAUTIONS, General**.)"

This proposed revision was faxed to Sanofi on October 21, 1999 (see attachment 1).

On March 4, 1999, Dr. Funmi Ajayi, Biopharmaceutics Team Leader, completed her review of NDA 14-214/S-050 and NDA 17-430/S-026 and found them to be acceptable.

NDA 14-214/S-051 and NDA 17-430/S-027 S-002 were submitted in response to an FDA letter to the company dated February 3, 1999 advising the company to incorporate class labeling revisions related to CNS toxicity, pediatric word changes and Videx® drug interaction (see attachment 2).

In an e-mail message dated September 20, 1999, Dr. Robert Hopkins, Clinical Team Leader, completed his review of NDA 14-214/S-051 and NDA 17-430/S-027 and concluded that these submissions were acceptable. He noted that the company had already incorporated the pediatric word changes in their May, 1998 label as we had requested. These changes were reported in the March 26, 1999 annual report.

On May 21, 1999, the company submitted a revised label incorporating their labeling revisions currently proposed for NegGram. On October 21, 1999, the company was advised to submit another revised label incorporating Dr. Cavaille-Coll's revision for the **PRECAUTIONS** section, **Geriatric Use** subsection. The revised label was dated October 26, 1999, received November 1, 1999, and included Dr. Cavaille-Coll's proposed revision for **PRECAUTIONS** section, **Geriatric Use** subsection.

Conclusions:
The FPL dated April, 1996 was visually compared to the package insert dated May, 1998. The only change in the May, 1998 label was the pediatric word change made in the **DOSAGE AND ADMINISTRATION** section of the label as follows:

NDA 14-214/S-050, S-051 and 17-430/S-026, S-027

> "Pediatric Patients. Until further experience is gained, NegGram should not be administered to infants younger than three months. Dosage in pediatric patients 12 years of age and under should be calculated on the basis of body weight. The recommended total daily dosage for initial therapy is 25 mg/lb/day (55 mg/kg/day), administered in four equally divided doses. For prolonged therapy, the total daily dose may be reduced to 15 mg/lb/day (33 mg/kg/day). NegGram Suspension or NegGram Caplets of 250 mg may be used. One 250 mg tablet is equivalent to one teaspoon (5 mL) of the suspension."

The package insert dated May, 1998 was then electronically compared to the revised draft labeling dated October 26, 1999. The changes were as follows:

1. PRECAUTIONS

• As we agreed, in the **Information for Patients** subsection, another paragraph was added as follows:

> "Patients should be advised that convulsions have been reported in patients taking quinolones, including Nalidixic acid, and to notify their physician before taking this drug if there is a history of this condition. Patients should be advised that mineral supplements, vitamins with iron or minerals, calcium-, aluminum-, magnesium-based antacids, sucralfate or Videx®, (Didanosine), chewable/buffered tablets of the pediatric power for oral solution should not be taken within the two-hour period before or within the two-hour period after taking nalidixic acid (see **Drug Interactions**)."

• As we agreed, in the **Drug Interactions** subsection, the "antacids" statement was revised to read:

> "Antacids containing magnesium, aluminum, or calcium; sucralfate or divalent or trivalent cations such as iron; multivitamins containing zinc; and Videx®, (Didanosine), chewable/buffered tablets or the pediatric power for oral solution may substantially interfere with the absorption of quinolones, resulting in systemic levels considerably lower than desired. These agents should not be taken within the two hour period before or within the two-hour period after nalidixic acid administration."

• As we agreed, a **Geriatric Use** subsection was added as follows:

> "Clinical studies of NegGram® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Caution should therefore be observed in using nalidixic acid in elderly patients. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients

are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See PRECAUTIONS, General.)"

2. DOSAGE AND ADMINISTRATION

- As we agreed, an antacid statement was added to this section as follows:

"Antacids containing calcium, magnesium, or aluminum; sucralfate; divalent or trivalent cations such as iron; multivitamins containing zinc; or Videx® (Didanosine), chewable/buffered tablets of the pediatric powder for oral solution should not be taken within the two-hour period before or within the two-hour period after taking nalidixic acid."

Recommendations:

An approval letter should be sent advising the applicant that NDA 14-214/S-050, S-051 and NDA 17-430/S-026, S-027 be approved. Final printed labeling (FPL) should be requested, and should be identical to the revised draft labeling dated October 26, 1999. The approval letter should note that the company logo was omitted from the revised draft labeling dated October 26, 1999 and should be included in the FPL.

Robin Anderson, RN, MBA
Regulatory Review Officer, HFD-590

Attachments:

1. Fax to company dated October 21, 1999 requesting revisions to the Geriatric Use section of the label
2. FDA letter to the sponsor regarding quinolone class labeling dated February 3, 1999

cc:
NDAs 14-214 and 17-430
HFD-590/Division File
HFD-590/R. Albrecht
HFD-590/ClinicalTL/Hopkins
HFD-590/MO/Cavaille-Coll
HFD-590/Biopharm TL/F. Ajayi
HFD-590/CPMS/Frank
HFD-590/PM/J.Fritsch
HF-2/MedWatch

Concurrence:

HFD-590/R. Albrecht 11/8/99
HFD-590/ClinicalTL/Hopkins 11/22/99
HFD-590/MO/Cavaille-Coll 11/1/99
HFD-590/Biopharm TL/F. Ajayi 11/8/99
HFD-590/CPMS/Frank

DFS keywords:
admin review
class quinolone
indic UTI, uncomp

APPEARS THIS WAY
ON ORIGINAL

/s/

Robin Anderson
11/23/1999 02:50:52 PM
INTERDISCIPLINARY

Ellen Frank
1/6/00 10:34:26 AM
CSO

Funmilayo Ajayif
3/10/00 04:20:07 PM
BIOPHARMACEUTICS

Marc Cavaille Coll
12/26/00 01:45:38 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: 10/21/99 Number of Pages (including cover sheet): 1
TO: Gary Lewis
COMPANY: Sanofi
FAX NUMBER: (212) 551-4912

MESSAGE: NDAs 14-241/S-050 and 17-430/S-026 (Neggram)

The clinical reviewer for these NDAs, Dr. Marc Cavaille-Coll, has requested that you make the following revision to the proposed Geriatric Use subsection for these NDAs as per the Federal Register notice:

[ ]

Please replace with:
"This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See PRECAUTIONS, General.)"

Please submit a revised label incorporating this change to these NDAs. Please also submit a desk copy of the revised label on diskette to me by 10/26/99 if possible. We hope to take action on these supplements within the next two weeks. Thank you.

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Robin Anderson, RN, MBA
TITLE: Regulatory Review Officer
TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 17-430/S-027

MAY 18 1999

Sanofi Pharmaceuticals, Inc.
90 Park Avenue, 6th Floor
New York, NY 10016

Attention: Amy Rubin, Associate Director, Drug Regulatory Affairs

Dear Ms Rubin:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: NegGram® (nalidixic acid) Suspension

NDA Number: 17-430

Supplement Number: S-027

Date of Supplement: April 27, 1999

Date of Receipt: April 30, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on June 29, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

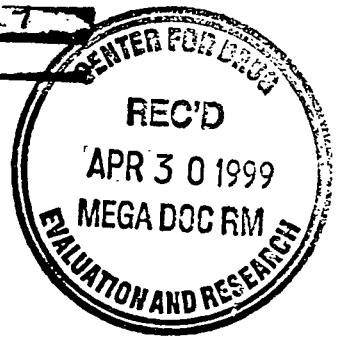
Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ORIGINAL sanofi

April 27, 1999

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NDA NO. 17430 REF NO. 027
NDA SUPPL FOR SCR



Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research, HFD 590
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 14-214 NegGram® (nalidixic acid, USP) Caplets
NDA 17-430 NegGram® (nalidixic acid, USP) Suspension
Supplement - Labeling

Dear Dr. Goldberger:

Per your letter of February 3, 1999, concerning additional labeling requirements for quinolones, enclosed are the draft labeling supplements for NegGram® (nalidixic acid, USP) Caplets and NegGram® Suspension, revised accordingly.

Sanofi has adopted the proposed revisions to the **Precautions** section, Information for Patients subsection and Drug Interactions subsection as well as the **Dosage and Administration** section.

Please note that the requested revision to the **Dosage and Administration** section to replace the word ~~~~ with 'Pediatric Patients' was incorporated in our last revision of the NegGram package inserts in May 1998.

Enclosed please find four copies of the draft labeling, revised as indicated.

This document consists of confidential and/or trade secret information subject to 18 U.S.C. 1905 and to which all claims of privilege and confidentiality are asserted in both statutory and common law.

Sanofi Pharmaceuticals, Inc.
90 Park Avenue, New York, NY 10016 - Tel.: (212) 551-4000 - Fax : (212) 551-4902

If you require any clarification or further information regarding this application, please do not hesitate to contact me at 212-551-4223.

Sincerely,

Laurie Lenkel

for Amy Rubin,
Associate Director
Drug Regulatory Affairs

Enclosure:
Four copies of draft labeling

Desk copy:
Ms. Mary Dempsey
Project Manager

APPEARS THIS WAY
ON ORIGINAL

HFD-590 Anderson

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 14-214
NDA 17-430

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

FEB - 3 1999

Amy Rubin, Associate Director
Drug Regulatory Affairs
Sanofi Pharmaceuticals, Inc.
90 Park Avenue
New York, NY 10016

Dear Ms. Rubin:

Reference is made to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for NegGram® (nalidixic acid) Caplets, NDA 14-214 and NegGram® (nalidixic acid) Suspension, NDA 17-430.

As part of the continuing review of labeling requirements for quinolones, and to provide pertinent information to the prescriber, the Division of Special Pathogen and Immunologic Drug Products proposes the **Precautions** section **Information for Patients** subsection be revised to include the following two paragraphs after the fourth paragraph of the advise list:

> " Patients should be advised that convulsions have been reported in patients taking quinolones, including Nalidixic acid, and to notify their physician before taking this drug if there is a history of this condition.
>
> Patients should be advised that mineral supplements, vitamins with iron or minerals, calcium-, aluminum-, magnesium-based antacids, sucralfate or Videx®, (Didanosine), chewable/buffered tablets or the pediatric power for oral solution should not be taken within the two-hour period before or within the two-hour period after taking naladixic acid (See **Drug Interactions**)."

Please revise the FIFTH paragraph of the **Drug Interactions** subsection of the **PRECAUTIONS** section of the labeling as follows:

"Antacids containing magnesium, aluminum, or calcium, sucralfate or divalent or trivalent cations such as iron; multivitamins containing zinc; and Videx®, (Didanosine), chewable/buffered tablets or the pediatric power for oral solution may substantially interfere with the absorption of quinolones resulting in systemic levels considerably lower than desired. These agents should not be taken within the two-hour period before or within the two-hour period after naladixic acid administration."

NDA 14-214
NDA 17-430

Please revise the **DOSAGE AND ADMINISTRATION** section of the labeling to include, before the instructions for *Adults* and *Pediatric Patients*, the following:

> "Antacids containing calcium, magnesium, or aluminum; sucralfate; divalent or trivalent cations such as iron; multivitamins containing zinc; or Videx®, (Didanosine), chewable/buffered tablets or the pediatric powder for oral solution should not be taken within the two-hour period before or within the two-hour period after taking naldixic acid."

Please revise the **DOSAGE AND ADMINISTRATION** section of the labeling to replace the word 'children' with 'Pediatric Patients', as follows:

> " *Pediatric Patients*. Until further experience is gained, NegGram should not be administered to infants younger than three months. Dosage in pediatric patients 12 years of age and under should be calculated on the basis of body weight. The recommended total daily dosage for initial therapy is 25 mg/lb/day (55 mg/kg/day), administered in four equally divided doses. For prolonged therapy, the total daily dose may be reduced to 15 mg/lb/day (33 mg/kg/day). NegGram Suspension or NegGram Caplets of 250 mg may be used. One 250 mg caplet is equivalent to one Teaspoon (5 ml) of the Suspension."

If you have any questions regarding the labeling revisions requested in this letter, please contact:

Mary Dempsey
Project Manager, at 301-827-2127.

Sincerely yours,

/S/

Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogens and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 17-430/S-026

DEC 15 1998

Sanofi Pharmaceuticals Inc.
90 Park Avenue, 6th floor
New York, NY 10016

Attention: Amy Rubin
Associate Director, DRA

Dear Ms. Rubin:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: NegGram® (nalidixic acid, USP) Suspension

NDA Number: 17-430

Supplement Number: S-026

Date of Supplement: December 4,1998

Date of Receipt: December 7, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on February 5,1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

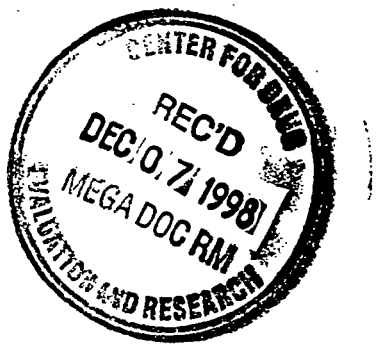
Ellen Frank

Ellen Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

sanofi

December 4, 1998

ORIGINAL



CERTIFIED MAIL
RETURN RECEIPT REQUESTED NDA NO. 17-430 REF. NO. 026

NDA SUPPL FOR SLR

Mark J. Goldberger, MD
Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room, HFD 590
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA 14-214 NegGram® (nalidixic acid, USP) Caplets
NDA 17-430 NegGram® (nalidixic acid, USP) Suspension
Specific Requirements on Content and Format of Labeling for Human Prescription Drugs
Addition of "Geriatric Use" Subsection in the Labeling
August 27, 1997 FR Volume 62 Number 166: 45313-45326
SUPPLEMENT

Dear Dr. Goldberger:

In accordance with the Federal Register Notice of August 27, 1997 (Vol. 62, No. 166) regarding the addition of the Geriatric Use Subsection in labeling, we are herein submitting labeling supplements for NegGram® (nalidixic acid, USP) Caplets, and NegGram® (nalidixic acid, USP) Suspension.

After a thorough review of the NDA, it is clear that there is insufficient data to determine the appropriate use of the drug in elderly patients. It is also unclear whether or not this population differs in their response from younger patients. Therefore, Sanofi has adapted the following language, based on the proposals in the Notice:

Geriatric Use
Clinical studies of NegGram® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Caution should therefore be observed in using nalidixic acid in elderly patients.

Sanofi Pharmaceuticals, Inc.
90 Park Avenue, New York, NY 10016 - Tel.: (212) 551-4000 - Fax : (212) 551-4902

December 4, 1998
NDA 14-214, 17-430 NegGram® (nalidixic acid, USP)
Addition of "Geriatric Use" Subsection in the Labeling
Supplement

[ ]

We have chosen not to include a dose selection statement since we do not recommend a dose range for this product as there is concern that underdosing may encourage bacterial resistance.

Enclosed, please find four copies of the draft labeling, revised as indicated.

This document consists of confidential and/or trade secret information subject to 18 U.S.C. 1905 and to which all claims of privilege and confidentiality are asserted in both statutory and common law.

If you require any clarification or further information regarding this application, please do not hesitate to contact me at 212.551.4223

Sincerely,

Amy Rubin
Associate Director
Drug Regulatory Affairs

enclosure:
Four copies of draft labeling

Desk copy:
Ms. Mary Dempsey
Project Manager