DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

NDA 14-214/S-053, S-055, S-056

Sanofi-Synthelabo
Attention: Michelle A. McGuinness
Senior Manager, Regulatory Operations, DRA
90 Park Ave.
New York, NY 10016

Dear Ms. McGuinness:

Please refer to your supplemental new drug applications, which were submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA #	Drug Product	Supplement Number	Letter Date	Receipt Date
14-214	NegGram® (nalidixic acid) Caplets, 500mg	S-053	April 8, 2003	April 16, 2003
		S-055	May 7, 2004	May 11, 2004
		S-056	May 7, 2004	May 11, 2004

We acknowledge receipt of your submissions dated May 22, 2003, March 10, 2004, and August 27, 2004 to S-053, and May 7, 2004, and August 27, 2004 to S-055 and S-056.

Your submission of August 27, 2004 constituted a complete response to the Division's October 10, 2003 action letter.

These supplemental new drug applications provide for the following revisions to the package insert (additions are <u>double underlined</u> and deletions are in ~~strikethrough~~):

1. <u>Caplets</u> was added after the drug name.

2. The following sentence was added under the drug name:

   <u>To reduce the development of drug-resistant bacteria and maintain the effectiveness of NegGram (nalidixic acid, USP) and other antibacterial drugs, NegGram should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.</u>

3. The following was added as the second paragraph of the **INDICATIONS AND USAGE** section:

   <u>To reduce the development of drug-resistant bacteria and maintain effectiveness of NegGram and other antibacterial drugs, NegGram should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered when selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.</u>

4. The **CONTRAINDICATIONS** section was revised as follows:

   NegGram is contraindicated in patients with known hypersensitivity to nalidixic acid or to related compounds, infants less than three months of age, and in patients with porphyria or a history of convulsive disorders. NegGram is contraindicated in patients undergoing concomitant therapy with melphalan or other related cancer chemotherapeutic alkylating agents because of serious gastrointestinal toxicity such as hemorrhagic ulcerative colitis or intestinal necrosis.

5. The following two paragraphs were added at the end of the **WARNINGS** section:

   Peripheral neuropathy: Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including nalidixic acid. Nalidixic acid should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, and/or motor strength in order to prevent the development of an irreversible condition.

   Tendon Effects: Ruptures of the shoulder, hand, Achilles tendon or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including nalidixic acid. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially in the elderly. Nalidixic acid should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been excluded. Tendon rupture can occur during or after therapy with quinolones, including nalidixic acid.

6. The following information was added at the end of the **PRECAUTIONS** section, **General** subsection:

   Cross-resistance between nalidixic acid and other quinolone derivatives such as oxolinic acid and cinoxacin has been observed.

   Caution should be observed in patients with glucose-6-phosphate dehydrogenase deficiency. (See ADVERSE REACTIONS).

   Prescribing NegGram in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

7. The following information was added at the end of the **PRECAUTIONS** section, **Information for Patients** subsection:

   Patients should be advised NegGram may be taken with or without meals. Patients should be advised to drink fluids liberally and not take antacids.

   Patients should be advised that quinolones may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reactions.

Quinolones may cause dizziness and light-headedness, therefore, patients should know how they react to NegGram before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.

Patients should be advised that quinolones may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking quinolones. Patients should be advised to avoid excessive sunlight or artificial ultraviolet light while receiving nalidixic acid and to discontinue therapy if phototoxicity occurs.

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 powder 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**).

Patients should be advised:

- that nalidixic acid may cause changes in the electrocardiogram (QTc interval prolongation)
- that nalidixic acid should be avoided in patients receiving class IA (e.g. quinidine, Procainamide) or class III (e.g. amiodarone, sotalol) antiarrhythmic agents
- that nalidixic acid should be used with caution in subjects receiving drugs that affect the QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants
- to inform their physicians of any personal or family history of QTc prolongation or proarrhythmic conditions such as hypokalemia, bradycardia or recent myocardial ischemia
- that peripheral neuropathies have been associated with nalidixic acid use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, they should discontinue treatment and contact their physicians.

Patients should be counseled that antibacterial drugs including NegGram should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When NegGram is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by NegGram or other antibacterial drugs in the future.

8. The **PRECAUTIONS** section, **Drug Interactions** subsection was revised as follows:

Elevated plasma levels of theophylline have been reported with concomitant quinolone use. There have been reports of theophylline-related side effects in patients on concomitant therapy with quinolones and theophylline. Therefore, monitoring of theophylline plasma levels should be considered and dosage of theophylline adjusted, as required.

Quinolones have been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and the prolongation of its plasma half-life.

Quinolones, including nalidixic acid, may enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation test should be closely monitored.

~~Nitrofurantoin interferes with the therapeutic~~ Since active proliferation of organisms is a necessary condition for its antibacterial activity, the action of nalidixic acid may be inhibited by the presence of other antibacterial substances, especially bacteriostatic agents such as tetracycline, chloramphenicol, or nitrofurantoin, which is antagonistic to nalidixic acid *in vitro*.

Probenecid inhibits the tubular secretion of nalidixic acid and may reduce its efficacy in the treatment of urinary tract infections while increasing the risk of systemic side effects.

Serious gastrointestinal toxicity has been associated with the concomitant use of nalidixic acid and the anti-cancer drug melphalan. (see CONTRAINDICATIONS)

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 powder 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.

Elevated serum levels of cyclosporine have been reported with the concomitant use of some quinolones and cyclosporine. Therefore, cyclosporine serum levels should be monitored and appropriate cyclosporine dosage adjustments made when these drugs are used concomitantly.

9. The **PRECAUTIONS** section, **Nursing Mothers** subsection was revised as follows:

~~It is not known whether NegGram is excreted in human milk. Because other drugs are excreted in human milk and because~~ Since nalidixic acid is excreted in breast milk, it is contraindicated during lactation.[1] ~~Because of the potential for serious adverse reactions in nursing infants from NegGram, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.~~

10. The **PRECAUTIONS** section, **Usage in Patients Under 18 Years of Age** subsection had the following sentence added:

Toxicological studies have shown that nalidixic acid and related drugs can produce erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of most species tested. No such joint lesions have been reported in humans to date. Nevertheless, until the significance of this finding is clarified, this drug should only be used in patients under 18 years of age when the potential benefit justifies the potential risk. If arthralgia occurs, treatment with nalidixic acid should be stopped. (See WARNINGS and ANIMAL PHARMACOLOGY.)

11. Anaphylactic shock was added to the **ADVERSE REACTIONS** section, **Allergic** subsection and Peripheral neuropathy was added to the **ADVERSE REACTIONS** section**, Other** subsection:

Allergic: rash, pruritus, urticaria, angioedema, eosinophilia, arthralgia with joint stiffness and swelling, and anaphylactoid reaction, including anaphylactic shock. Erythema Multiforme and Stevens-Johnson syndrome have been reported with nalidixic acid and other drugs in this class. Rash was the most frequently reported adverse reaction. Photosensitivity reactions consisting of erythema and bullae on exposed skin surfaces usually resolve completely in 2 weeks to 2 months after NegGram is discontinued; however, bullae may continue to appear with successive exposures to sunlight or with mild skin trauma for up to 3 months after discontinuation of drug. (See PRECAUTIONS.)

Other: rarely, cholestasis, paresthesia, metabolic acidosis, thrombocytopenia, leukopenia, or hemolytic anemia, sometimes associated with glucose 6-phosphate dehydrogenase deficiency and peripheral neuropathy.

12. The **OVERDOSAGE** section, **Treatment** subsection had the following deletion:

Treatment: Reactions are short-lived (two to three hours) because the drug is rapidly excreted. ~~If overdosage is noted early, gastric lavage is indicated.~~ If absorption has occurred, increased fluid administration is advisable and supportive measures such as oxygen and means of artificial respiration should be available. Although anticonvulsant therapy has not been used in the few instances of overdosage reported, it may be indicated in a severe case.

13. The **HOW SUPPLIED** section was revised as follows:

~~Caplets of 1 g, light buff-colored capsule-shaped tablets,~~
~~bottles of 100 (NDC 0024-1323-04)~~ NegGram (nalidixic acid, USP) is supplied as:
Caplets of 500 mg, light buff-colored capsule-shaped tablets,
bottles of 56 (NDC 0024-1322-03)
~~500 (NDC 0024-1322-06)~~
~~Caplets of 250 mg, light buff-colored capsule-shaped tablets,~~
~~bottles of 56 (NDC 0024-1321-03)~~
Store at room temperature, up to 30° C (86° F).

We have completed the review of these supplemental new drug applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text (enclosed). Accordingly, this supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted August 27, 2004).

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. For administrative purposes, these submissions should be designated **"FPL for approved supplement NDA 14-214/S-053, S-055, S-056**." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Christine Lincoln, RN, MS, MBA, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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
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