DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 050420/S-073
NDA 050627/S-012

SUPPLEMENT APPROVAL

sanofi-aventis U.S. LLC
Attention: JoBeth Crimmins
U.S. Regulatory Affairs Marketed Products
55 Corporate Drive
Bridgewater, NJ 08807

Dear Ms. Crimmins:

Please refer to your Supplemental New Drug Applications (sNDA) dated November 7, 2008, received November 10, 2008 for NDA 050420/S-073 and your submission dated November 11, 2008, received November 12, 2008 for NDA 050627/S-012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rifadin® (rifampin capsules USP), 150 mg & 300 mg and Rifadin® (rifampin for injection USP) IV, 600 mg respectively.

We acknowledge receipt of your amendments dated May 11, 2010 and November 4, 2010.

The May 11, 2010, submission constituted a complete response to our May 8, 2009, action letter.

This "Prior Approval" supplemental new drug applications propose the following revisions to the package insert (~~strikethrough~~ = deleted information and underline = added information):

1. In the **CLINICAL PHARMACOLOGY/Oral Administration** subsection, the third and fourth paragraph are revised as follows:

   In healthy adults, the mean biological half-life of rifampin in serum averages 3.35 ± 0.66 hours after a 600 mg oral dose, with increases up to 5.08 ± 2.45 hours reported after a 900 mg dose. With repeated administration, the half-life decreases and reaches average values of approximately 2 to 3 hours. The half-life does not differ in patients with renal failure at doses not exceeding 600 mg daily, and consequently, no dosage adjustment is required. The half-life of rifampin at a dose of 720 mg daily has not been established in patients with renal failure. Following a single 900 mg oral dose of rifampin in patients with varying degrees of renal insufficiency, the mean half-life increased from 3.6 hours in healthy adults to 5.0, 7.3, and 11.0 hours in patients with glomerular filtration rates of 30 to 50 mL/min, less than 30 mL/min, and in anuric patients, respectively. Refer to the WARNINGS section for information regarding patients with hepatic insufficiency.

   After absorption, r~~R~~ifampin is rapidly eliminated in the bile, and an enterohepatic circulation ensues. During this process, rifampin undergoes progressive deacetylation so

that nearly all the drug in the bile is in this form in about 6 hours. This metabolite ~~is microbiologically active~~ has antibacterial activity. Intestinal reabsorption is reduced by deacetylation, and elimination is facilitated. Up to 30% of a dose is excreted in the urine, with about half of this being unchanged drug.

2. The **CLINICAL PHARMACOLOGY/Microbiology** subsection is revised as follows:

Microbiology
Mechanism of Action
Rifampin inhibits DNA-dependent RNA polymerase activity in susceptible ~~cells~~ *Mycobacterium tuberculosis* organisms. Specifically, it interacts with bacterial RNA polymerase but does not inhibit the mammalian enzyme. ~~Rifampin at therapeutic levels has demonstrated bactericidal activity against both intracellular and extracellular *Mycobacterium tuberculosis* organisms.~~

Drug Resistance
Organisms resistant to rifampin are likely to be resistant to other rifamycins. ~~Rifampin has bactericidal activity against slow and intermittently growing *M tuberculosis* organisms. It also has significant activity against *Neisseria meningitidis* isolates (see INDICATIONS AND USAGE).~~

In the treatment of both tuberculosis and the meningococcal carrier state (see INDICATIONS AND USAGE), the small number of resistant cells present within large populations of susceptible cells can rapidly become predominant. In addition, resistance to rifampin has been determined to occur as single-step mutations of the DNA-dependent RNA polymerase. Since resistance can emerge rapidly, appropriate susceptibility tests should be performed in the event of persistent positive cultures.

Activity *in vitro* and *in vivo*
Rifampin has bactericidal activity *in vitro* against slow and intermittently growing *M tuberculosis* organisms.

Rifampin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Aerobic Gram-Negative Microorganisms:
Neisseria meningitidis

"Other" Microorganisms:
Mycobacterium tuberculosis

The following *in vitro* data are available, but their clinical significance is unknown.

Rifampin exhibits *in vitro* activity against most strains of the following microorganisms; however, the safety and effectiveness of rifampin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic Gram-Positive Microorganisms:
Staphylococcus aureus (including Methicillin-Resistant *S. aureus*/MRSA)
Staphylococcus epidermidis

Aerobic Gram-Negative Microorganisms:
Haemophilus influenzae

"Other" Microorganisms:
Mycobacterium leprae

ß-lactamase production should have no effect on rifampin activity.

3. The **CONTRAINDICATIONS** section is revised as follows:

CONTRAINDICATIONS
RIFADIN ~~Rifadin~~ is contraindicated in patients with a history of hypersensitivity to rifampin or any of the components, or to any of the rifamycins. (See WARNINGS.)

Rifampin is contraindicated in patients who are also receiving ritonavir-boosted saquinavir due to an increased risk of severe hepatocellular toxicity. (See PRECAUTIONS, Drug Interactions.)

Rifampin is contraindicated in patients who are also receiving atazanavir, darunavir, fosamprenavir, saquinavir, or tipranavir due to the potential of rifampin to substantially decrease plasma concentrations of these antiviral drugs, which may result in loss of antiviral efficacy and/or development of viral resistance.

4. In the **PRECAUTIONS/General** subsection, a new sentence is added at the beginning of the subsection and the 4th paragraph is revised as follows:

General
RIFADIN should be used with caution in patients with a history of diabetes mellitus, as diabetes management may be more difficult.

Prescribing rifampin 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.

For the treatment of tuberculosis, rifampin is usually administered on a daily basis. Doses of rifampin greater than 600 mg given once or twice weekly have resulted in a higher incidence of adverse reactions, including the "flu syndrome" (fever, chills and malaise),

hematopoietic reactions (leukopenia, thrombocytopenia, or acute hemolytic anemia), cutaneous, gastrointestinal, and hepatic reactions, shortness of breath, shock, anaphylaxis, and renal failure. Recent studies indicate that regimens using twice-weekly doses of rifampin 600 mg plus isoniazid 15 mg/kg are much better tolerated.

~~Intermittent therapy may be used if the patient cannot (or will~~ Rifampin is not~~)~~ ~~self-administer drugs on a daily basis. Patients on~~ recommended for intermittent therapy; the patient should ~~be closely monitored for compliance and~~ cautioned against intentional or accidental interruption ~~of prescribed therapy, because of~~ the ~~increased risk of serious adverse~~ daily dosage regimen since rare renal hypersensitivity reactions have been reported when therapy was resumed in such cases.

Rifampin has enzyme induction properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones, and vitamin D. Rifampin and isoniazid have been reported to alter vitamin D metabolism. In some cases, reduced levels of circulating 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D have been accompanied by reduced serum calcium and phosphate, and elevated parathyroid hormone.

5. The **PRECAUTIONS/Drug Interactions** subsection is revised as follows:

~~ENZYME INDCUTION:~~ Healthy subjects who received rifampin 600 mg once daily concomitantly with saquinavir 1000 mg/ritonavir 100 mg twice daily (ritonavir-boosted saquinavir) developed severe hepatocellular toxicity. Therefore, concomitant use of these medications is contraindicated. (See CONTRAINDICATIONS.)

Enzyme Induction: Rifampin is known to induce certain cytochrome P-450 enzymes. Administration of rifampin with drugs that undergo biotransformation through these metabolic pathways may accelerate elimination of coadministered drugs. To maintain optimum therapeutic blood levels, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping concomitantly administered rifampin.

Rifampin has been reported to substantially decrease the plasma concentrations of the following antiviral drugs: atazanavir, darunavir, fosamprenavir, saquinavir, and tipranavir. These antiviral drugs must not be co-administered with rifampin. (See CONTRAINDICATIONS.)

Rifampin has been reported to accelerate the metabolism of the following drugs: anticonvulsants (eg, phenytoin), digitoxin, antiarrhythmics (eg, disopyramide, mexiletine, quinidine, tocainide), oral anticoagulants, antifungals (eg, fluconazole, itraconazole, ketoconazole), barbiturates, beta-blockers, calcium channel blockers (eg, diltiazem, nifedipine, verapamil), chloramphenicol, clarithromycin, corticosteroids, cyclosporine, cardiac glycoside preparations, clofibrate, oral or other systemic hormonal contraceptives, dapsone, diazepam, doxycycline, fluoroquinolones (eg, ciprofloxacin), haloperidol, oral hypoglycemic agents (sulfonylureas), levothyroxine, methadone,

narcotic analgesics, ~~nortriptyline,~~ progestins, quinine, tacrolimus, theophylline, tricyclic antidepressants (eg, amitriptyline, nortriptyline) and zidovudine. It may be necessary to adjust the dosages of these drugs if they are given concurrently with rifampin.

Patients using oral or other systemic hormonal contraceptives should be advised to change to nonhormonal methods of birth control during rifampin therapy.

Rifampin has been observed to increase the requirements for anticoagulant drugs of the coumarin type. In patients receiving anticoagulants and rifampin concurrently, it is recommended that the prothrombin time be performed daily or as frequently as necessary to establish and maintain the required dose of anticoagulant.

~~Diabetes may become more difficult to control.~~

~~OTHER INTERACTIONS~~Other Interactions: When the two drugs were taken concomitantly, decreased concentrations of atovaquone and increased concentrations of rifampin were observed.

6. In the **PRECAUTIONS/Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, the third paragraph is revised as follows:

There was no evidence of mutagenicity in bacteria, *Drosophila melanogaster,* or mice. An increase in ~~chromotid~~ chromatid breaks was noted when whole blood cell cultures were treated with rifampin. Increased frequency of chromosomal aberrations was observed *in vitro* in lymphocytes obtained from patients treated with combinations of rifampin, isoniazid, and pyrazinamide and combinations of streptomycin, rifampin, isoniazid, and pyrazinamide.

7. In the **ADVERSE REACTIONS/Gastrointestinal** subsection, a new subsection titled Hepatic, and a new first sentence are added as follows:

Hepatic
Transient abnormalities in liver function tests (e.g., elevations in serum bilirubin, BSP, alkaline phosphatase, serum transaminases) have been observed. Rarely, hepatitis or a shock-like syndrome with hepatic involvement and abnormal liver function tests has been reported.

8. The **ADVERSE REACTIONS/Central Nervous System** subsection is revised as follows:

Central Nervous System
Headache, fever, drowsiness, fatigue, ataxia, dizziness, inability to concentrate, mental confusion, behavioral changes, muscular weakness, pains in extremities, and generalized numbness have been observed.

Psychoses have been rarely reported.

Rare reports of myopathy have also been observed.

9. In the he **ADVERSE REACTIONS Miscellaneous** subsection, the first sentence is deleted as follows:

Miscellaneous
~~Rare reports of myopathy and muscular weakness have also been observed.~~

Edema of the face and extremities has been reported. Other reactions reported to have occurred with intermittent dosage regimens include "flu syndrome" (such as episodes of fever, chills, headache, dizziness, and bone pain), shortness of breath, wheezing, decrease in blood pressure and shock. The "flu syndrome" may also appear if rifampin is taken irregularly by the patient or if daily administration is resumed after a drug free interval.

10. In the **OVERDOSAGE/Signs and Symptoms** subsection, a second paragraph is added as follows:

Signs and Symptoms
Nausea, vomiting, abdominal pain, pruritus, headache, and increasing lethargy will probably occur within a short time after ingestion; unconsciousness may occur when there is severe hepatic disease. Transient increases in liver enzymes and/or

bilirubin may occur. Brownish-red or orange discoloration of the skin, urine, sweat, saliva, tears, and feces will occur, and its intensity is proportional to the amount ingested.

Liver enlargement, possibly with tenderness, can develop within a few hours after severe overdosage; bilirubin levels may increase and jaundice may develop rapidly. Hepatic involvement may be more marked in patients with prior impairment of hepatic function. Other physical findings remain essentially normal. A direct effect upon the hematopoietic system, electrolyte levels, or acid-base balance is unlikely.

11. The **OVERDOSAGE/Treatment** subsection is revised as follows:

Treatment
Intensive support measures should be instituted and individual symptoms treated as they arise. The airway should be secured and adequate respiratory exchange established. Since nausea and vomiting are likely to be present, gastric lavage within the first 2 to 3 hours after ingestion is probably preferable to induction of emesis. Following evacuation of the gastric contents, the instillation of activated charcoal slurry into the stomach may help absorb any remaining drug from the gastrointestinal tract. Antiemetic medication may be required to control severe nausea and vomiting.

Active diuresis (with measured intake and output) will help promote excretion of the drug.

~~Hemodialysis may be of value in some patients.~~

For severe cases, extracorporeal hemodialysis may be required. If this is not available, peritoneal dialysis can be used along with forced diuresis.

We also note that your proposed labeling contains editorial revisions including an update of the References section of the package. These changes do not require our approval.

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.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements and any 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 from 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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

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 Dr. Hyun Son Safety Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, M.D., M.P.H.
Deputy Director for Safety
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/

OZLEM A BELEN
11/10/2010