



NDA 50705/S-007

**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 Application (sNDA) dated November 12, 2008, received November 13, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rifater<sup>®</sup> (rifampin, isoniazid and pyrazinamide), Tablets, 120 mg rifampin, 50 mg isoniazid, 300 mg pyrazinamide.

We acknowledge receipt of your amendments dated May 14, 2010, July 27, 2010, November 8, 2010 and November 10, 2010.

The May 14, 2010, submission constituted a complete response to our May 8, 2009, action letter.

This “Prior Approval” supplemental new drug application proposes the following revisions to the package insert (~~strike through~~ = deleted information and underline = added information):

1. In the **DESCRIPTION/Isoniazid** subsection, the first paragraph has been revised as follows:

**Isoniazid**

Isoniazid is the ~~hydroxide~~ hydrazide of isonicotinic acid. It is a colorless or white crystalline powder or white crystals. It is odorless and slowly affected by exposure to air and light. It is freely soluble in water, sparingly soluble in alcohol and slightly soluble in chloroform and in ether. Its molecular weight is 137.14 and its chemical formula is C<sub>6</sub>H<sub>7</sub>N<sub>3</sub>O.

2. The **CLINICAL PHARMACOLOGY** has been revised as follows. We note that these revisions include a relocation of information originally described after information on **Pyrazinamide**, and just before the **Microbiology** subsection.

**General**

~~Rifampin.~~ In a single-dose bioavailability study of five RIFATER tablets (Treatment A, n=23) versus RIFADIN 600 mg, isoniazid 250 mg, and pyrazinamide 1500 mg

(Treatment B, n=24) administered concurrently in healthy subjects, there was no difference in extent of absorption, as measured by the area under the plasma concentration versus time curve (AUC), of all three components. However, the mean peak plasma concentration of rifampin was approximately 18% lower following the single-dose administration of RIFATER tablets as compared to RIFADIN administered in combination with pyrazinamide and isoniazid. Mean (±SD) pharmacokinetic parameters are summarized in the following table.

<u>Parameter</u>	<u>C<sub>max</sub></u> <u>(mcg/mL)</u>		<u>Half-life</u> <u>(hr)</u>		<u>Apparent Oral</u> <u>Clearance</u> <u>(L/hr)</u>		<u>Bioavail</u> <u>=</u> <u>ability</u> <u>(%)</u>
	<u>A</u>	<u>B</u>	<u>A</u>	<u>B</u>	<u>A</u>	<u>B</u>	<u>A</u>
<u>Isoniazid</u>	<u>3.09</u> <u>± 0.88</u>	<u>3.14</u> <u>± 0.92</u>	<u>2.80</u> <u>± 1.02</u>	<u>2.80</u> <u>± 1.11</u>	<u>24.02</u> <u>±15.29</u>	<u>25.72</u> <u>±18.38</u>	<u>100.6</u> <u>±16.6</u>
<u>Rifampin</u>	<u>11.04</u> <u>± 3.08</u>	<u>13.61</u> <u>± 3.96</u>	<u>3.19</u> <u>± 0.63</u>	<u>3.41</u> <u>± 0.86</u>	<u>9.62</u> <u>± 3.00</u>	<u>8.30</u> <u>± 2.50</u>	<u>88.8</u> <u>±16.5</u>
<u>Pyrazinamide</u>	<u>28.02</u> <u>± 4.52</u>	<u>29.21</u> <u>± 4.35</u>	<u>10.04</u> <u>± 1.54</u>	<u>10.08</u> <u>± 1.29</u>	<u>3.82</u> <u>± 0.65</u>	<u>3.70</u> <u>± 0.59</u>	<u>96.8</u> <u>± 7.6</u>

The effect of food on the pharmacokinetics of RIFATER tablets was not studied.

### **Rifampin**

Rifampin is readily absorbed from the gastrointestinal tract. Peak serum levels in normal healthy adults and pediatric populations vary widely from individual to individual. Following a single 600 mg oral dose of rifampin in healthy adults, the peak serum level averages 7 mcg/mL but may vary from 4 to 32 mcg/mL. Absorption of rifampin is reduced by about 30% when the drug is ingested with food.

In normal healthy adults, the biological half-life of rifampin in serum averages about 3.35 ± 0.66 hours after a 600 mg oral dose, with increases up to 5.408 ± 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 normal subjects healthy adults to 5.0, 7.3, and 11.0 hours in patients with glomerular filtration rates of 30-50 mL/min, less than 30 mL/min, and in anuric patients, respectively. Refer to the WARNINGS section for information regarding patients with hepatic insufficiency.

Rifampin is widely distributed throughout the body. It is present in effective concentrations in many organs and body fluids, including cerebrospinal fluid.

Rifampin is about 80% protein bound. Most of the unbound fraction is not ionized and therefore is diffused freely in tissues.

After absorption, rifampin 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 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 as unchanged drug.

**Pediatrics:** In one study, pediatric patients 6 to 58 months old were given rifampin suspended in simple syrup or as dry powder mixed with applesauce at a dose of 10 mg/kg body weight. Peak serum concentrations of  $10.7 \pm 3.7$  and  $11.5 \pm 5.1$  mcg/mL were obtained 1 hour after preprandial ingestion of the drug suspension and the applesauce mixture, respectively. After the administration of either preparation, the  $t_{1/2}$  of rifampin averaged 2.9 hours. It should be noted that in other studies in pediatric populations, at doses of 10 mg/kg body weight, mean peak serum concentrations of 3.5 mcg/mL to 15 mcg/mL have been reported.

### **Isoniazid**

After oral administration, isoniazid is readily absorbed from the GI tract and produces peak blood levels within 1 to 2 hours which decline to 50% or less within 6 hours. It diffuses readily into all body fluids (cerebrospinal, pleural, and ascitic fluids), tissues, organs, and excreta (saliva, sputum, and feces). Isoniazid is not substantially bound to plasma proteins. The drug also passes through the placental barrier and into milk in concentrations comparable to those in the plasma. The plasma half-life of isoniazid in patients with normal renal and hepatic function ranges from 1-4 hours, depending on the rate of metabolism. From 50% to 70% of a dose of isoniazid is excreted in the urine within 24 hours, mostly as metabolites.

Within 24 hours, approximately 70% of an oral dose of pyrazinamide is excreted in urine, mainly by glomerular filtration. About 4% to 14% of the dose is excreted as unchanged drug; the remainder is excreted as metabolites.

### **RIFATER**

~~In a single-dose bioavailability study of five RIFATER tablets (Treatment A, n=23) versus RIFADIN 600 mg, isoniazid 250 mg, and pyrazinamide 1500 mg (Treatment B, n=24) administered concurrently in normal subjects, there was no difference in extent of absorption, as measured by the area under the plasma concentration versus time curve (AUC), of all three components. However, the mean peak plasma concentration of rifampin was approximately 18% lower following the single-dose administration of RIFATER tablets as compared to RIFADIN administered in combination with pyrazinamide and isoniazid. Mean ( $\pm$ SD) pharmacokinetic parameters are summarized in the following table.~~

Parameter	$C_{max}$ ( $\mu\text{g/mL}$ )		Half-life (hr)		Apparent Oral Clearance (L/hr)		Bioavail- ability (%)
	-A	-B	-A	-B	-A	-B	
Treatment	-A	-B	-A	-B	-A	-B	-A
Isoniazid	-3.09 $\pm$ 0.88	-3.14 $\pm$ 0.92	-2.80 $\pm$ 1.02	-2.80 $\pm$ 1.11	-24.02 $\pm$ 15.29	25.72 $\pm$ 18.38	-100.6 $\pm$ 16.6
Rifampin	-11.04 $\pm$ 3.08	-13.61 $\pm$ 3.96	-3.19 $\pm$ 0.63	-3.41 $\pm$ 0.86	-9.62 $\pm$ 3.00	-8.30 $\pm$ 2.50	-88.8 $\pm$ 16.5
Pyrazinamide	-28.02 $\pm$ 4.52	-29.21 $\pm$ 4.35	-10.04 $\pm$ 1.54	-10.08 $\pm$ 1.29	-3.82 $\pm$ 0.65	-3.70 $\pm$ 0.59	-96.8 $\pm$ 7.6

The effect of food on the pharmacokinetics of RIFATER tablets was not studied.

### Microbiology

Rifampin, isoniazid, and pyrazinamide at therapeutic levels have demonstrated bactericidal activity against both intracellular and extracellular *Mycobacterium tuberculosis* organisms.

### Mechanism of Action

#### Rifampin:

Rifampin inhibits DNA-dependent RNA polymerase activity in susceptible *Mycobacterium tuberculosis* organisms. Specifically, it interacts with bacterial RNA polymerase, but does not inhibit the mammalian enzyme. Organisms resistant to rifampin are likely to be resistant to other rifamycins.

#### Isoniazid

Isoniazid kills actively growing tubercle bacilli by inhibiting the biosynthesis of mycolic acids which are major components of the cell wall of *Mycobacterium tuberculosis*.

#### Pyrazinamide

The exact mechanism of action by which pyrazinamide inhibits the growth of *Mycobacterium tuberculosis* organisms is unknown.

### Drug Resistance

Organisms resistant to rifampin are likely to be resistant to other rifamycins.  $\beta$ -lactamase production should have no effect on rifampin activity.

**In the treatment of tuberculosis, 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 studies**

Rifampin, isoniazid, and pyrazinamide at therapeutic levels have demonstrated that pyrazinamide bactericidal activity against both intracellular and extracellular *Mycobacterium tuberculosis* organisms (see INDICATIONS AND USAGE section).

Pyrazinamide alone is only active at a slightly acidic pH (pH 5.5) *in vitro* and *in vivo*. Isoniazid kills actively growing tubercle bacilli.

**Susceptibility Testing**

Prior to initiation of therapy, appropriate specimens should be collected for identification of the infecting organism and *in vitro* susceptibility tests.

*In vitro* testing for *Mycobacterium tuberculosis* isolates

Two standardized *in vitro* susceptibility methods are available for testing isoniazide, rifampin, and pyrazinamid against *Mycobacterium tuberculosis* organisms. ....

3. In the **CONTRAINDICATIONS** section, the first paragraph is revised and a new subsection titled **Rifampin** has been added as follows:

RIFATER is contraindicated in patients with a history of hypersensitivity to rifampin, isoniazid, pyrazinamide or any of the components, or to any of the rifamycins.

**Rifampin**

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. The **PRECAUTIONS/Rifampin** subsection has been revised as follows:

**Rifampin**

For treatment of tuberculosis, rifampin is usually administered on a daily basis. Doses of rifampin (>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.

The patient should be advised that the reliability of oral contraceptives may be affected; consideration should be given to using alternative contraceptive measures. Rifampin is not recommended for intermittent therapy; the patient should be cautioned against intentional or accidental interruption of the 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.

5. In the **PRECAUTIONS/Information for Patients** subsection, a third paragraph is added and the fourth paragraph has been revised as follows:

The patient should be advised that the reliability of oral or other systemic hormonal contraceptives may be affected; consideration should be given to using alternative contraceptive measures.

Patients should be instructed to take RIFATER either 1 hour before or 2 hours after a meal with a full glass of water.

6. The **PRECAUTIONS/Laboratory Tests** subsection has been revised as follows:

~~A COMPLETE BLOOD COUNT (CBC) LIVER FUNCTION TESTS, AND BLOOD URIC ACID DETERMINATIONS SHOULD BE OBTAINED PRIOR TO INSTITUTING THERAPY AND PERIODICALLY THROUGHOUT THE COURSE OF THERAPY. BECAUSE OF A POSSIBLE TRANSIENT RISE IN TRANSAMINASE AND BILIRUBIN VALUES, BLOOD FOR BASELINE CHILNICAL CHEMISTRIES SHOULD BE OBTAINED BEFORE RIFATER DOSING.~~

Adults treated for tuberculosis with RIFATER should have baseline measurements of hepatic enzymes, bilirubin, serum creatinine, a complete blood count (CBC) and platelet count (or estimate), and blood uric acid.

Patients should be seen at least monthly during therapy and should be specifically questioned concerning symptoms associated with adverse reactions. All patients with abnormalities should have follow-up, including laboratory testing, if necessary. Routine laboratory monitoring for toxicity in people with normal baseline measurements is generally not necessary.

7. The **PRECAUTIONS/Drug Interactions** subsection has been revised as follows:

## **Rifampin**

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. Coadministration of RIFATER, because it contains rifampin, with drugs that undergo biotransformation through these metabolic pathways may accelerate elimination. 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, fluoroquinolones (eg, ciprofloxacin), corticosteroids, cyclosporine, cardiac glycoside preparations, clofibrate, oral or other systemic hormonal contraceptives, dapsone, diazepam, doxycycline, haloperidol, oral hypoglycemic agents (sulfonylureas), levothyroxine, methadone, narcotic analgesics, ~~nortriptyline~~, progestins, and quinine, tacrolimus, theophylline, tricyclic antidepressants (eg, amitriptyline, ~~nortriptyline~~), and zidovudine. It may be necessary to adjust dosages of these drugs if they are given concurrently with RIFATER since it contains 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 RIFATER 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.

When the two drugs were taken concomitantly, decreased concentrations of atovaquone and increased concentrations of rifampin were observed.

Concurrent use of ketoconazole and rifampin has resulted in decreased serum concentration of both drugs. Concurrent use of rifampin and enalapril has resulted in decreased concentrations of enalaprilat, the active metabolite of enalapril. Since RIFATER contains rifampin, dosage adjustments should be made if RIFATER is

concurrently administered with ketoconazole or enalapril if indicated by patient's clinical condition.

8. The **PRECAUTIONS/Drug/Laboratory Test Interactions/Rifampin** subsection, a new first paragraph has been revised as follows:

#### **Rifampin**

Cross-reactivity and false-positive urine screening tests for opiates have been reported in patients receiving rifampin when using the KIMS (Kinetic Interaction of Microparticles in Solution) method (eg, Abuscreen OnLine opiates assay; Roche Diagnostic Systems). Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish rifampin from opiates.

9. The **PRECAUTIONS/Pregnancy-Teratogenic Effects/Rifampin** subsection, the first paragraph has been revised as follows:

Rifampin has been shown to be teratogenic in rodents given oral doses of rifampin 15 to 25 times the human dose. Although rifampin has been reported to cross the placental barrier and appear in cord blood, the effect of rifampin, alone or in combination with other antituberculosis drugs, on the human fetus is not known. Isolated cases of fetal malformations have been reported; however, there are no adequate and well-controlled studies in pregnant women. An increase in congenital malformations, primarily spina bifida and cleft palate, has been reported in the offspring of rodents given oral doses of 150 to 250 mg/kg/day of rifampin during pregnancy. The incidence of these anomalies was dose-dependent. When rifampin was given to pregnant rabbits in doses up to 20 times the usual daily human dose, imperfect osteogenesis and embryotoxicity were reported.

10. The **ADVERSE REACTIONS/Reported for Individual Components** subsection has been revised as follows:

#### **Rifampin**

**Gastrointestinal:** Heartburn, epigastric distress, anorexia, nausea, vomiting, jaundice, flatulence, cramps, and diarrhea have been noted in some patients. Although *Clostridium difficile* has been shown *in vitro* to be sensitive to rifampin, pseudomembranous colitis has been reported with the use of rifampin (and other broad spectrum antibiotics). Therefore, it is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use.

**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 shocklike syndrome with hepatic involvement and abnormal liver function tests has been reported.

**Hematologic:** Thrombocytopenia has occurred primarily with high dose intermittent therapy, but has also been noted after resumption of interrupted treatment. It rarely occurs during well-supervised daily therapy. This effect is reversible if the drug is discontinued as soon as purpura occurs. Cerebral hemorrhage and fatalities have been reported when rifampin administration has been continued or resumed after the appearance of purpura.

Rare reports of disseminated intravascular coagulation have been observed.

Leukopenia, hemolytic anemia, and decreased hemoglobin have been observed.

Agranulocytosis has been reported rarely.

**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.

**Ocular:** Visual disturbances have been observed.

**Endocrine:** Menstrual disturbances have been observed.

Rare reports of adrenal insufficiency in patients with compromised adrenal function have been observed.

**Renal:** Elevations in BUN and serum uric acid have been reported. Rarely, hemolysis, hemoglobinuria, hematuria, interstitial nephritis, acute tubular necrosis, renal insufficiency, and acute renal failure have been noted. These are generally considered to be hypersensitivity reactions. They usually occur during intermittent therapy or when treatment is resumed following intentional or accidental interruption of a daily dosage regimen, and are reversible when rifampin is discontinued and appropriate therapy instituted.

**Dermatologic:** Cutaneous reactions are mild and self-limiting and do not appear to be hypersensitivity reactions. Typically, they consist of flushing and itching with or without a rash. More serious cutaneous reactions which may be due to hypersensitivity occur but are uncommon.

**Hypersensitivity Reactions:** Occasionally pruritus, urticaria, rash, pemphigoid reaction, erythema multiforme including Stevens-Johnson Syndrome, toxic epidermal necrolysis, vasculitis, eosinophilia, sore mouth, sore tongue and conjunctivitis have been observed.

Anaphylaxis has been reported rarely.

Although rifampin has been reported to have an immunosuppressive effect in some animal experiments, available human data indicate that this has no clinical significance.

### **Isoniazid**

The most frequent reactions are those affecting the nervous system and the liver. (See the boxed WARNING)

**Nervous System:** Peripheral neuropathy is the most common toxic effect. It is dose-related, occurs most often in the malnourished and in those predisposed to neuritis (eg, alcoholics and diabetics), and is usually preceded by paresthesia of the feet and hands. The incidence is higher in “slow inactivators.”

Other neurotoxic effects, which are uncommon with conventional doses, are convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment, and toxic psychosis.

**Gastrointestinal:** Pancreatitis, ~~n~~Nausea, vomiting, and epigastric distress.

**Hepatic:** Elevated serum transaminases (SGOT, SGPT), bilirubinemia, bilirubinuria, jaundice, and occasionally severe and sometimes fatal hepatitis. The common prodromal symptoms are anorexia, nausea, vomiting, fatigue, malaise, and weakness. Mild and transient elevation of serum transaminase levels occurs in 10 to 20% of persons taking isoniazid. The abnormality usually occurs in the first 4 to 6 months of treatment but can occur at any time during therapy. In most instances, enzyme levels return to normal with no necessity to discontinue medication. In occasional instances, progressive liver damage occurs, with accompanying symptoms. In these cases, the drug should be discontinued immediately. The frequency of progressive liver damage increases with age. It is rare in persons under 20, but occurs in up to 2.3% of those over 50 years of age.

**Hematologic:** Agranulocytosis; hemolytic, sideroblastic, or aplastic anemia; thrombocytopenia; and eosinophilia.

**Hypersensitivity Reactions:** Fever, skin eruptions (morbilliform, maculopapular, purpuric, or exfoliative), lymphadenopathy, anaphylactic reactions, Stevens-Johnson syndrome, and vasculitis.

11. The **OVERDOSAGE/Acute Toxicity/Rifampin** subsection has been revised as follows:

### **Acute Toxicity Rifampin**

~~Non-fatal overdoses with as high as 12g of rifampin have been reported.~~

~~One case of fatal overdose is known: A 26-year-old man died after self-administering 60 g of rifampin.~~

The minimum acute lethal or toxic dose is not well established. However, nonfatal acute overdoses in adults have been reported with doses ranging from 9 to 12 gm rifampin. Fatal acute overdoses in adults have been reported with doses ranging from 14 to 60 gm. Alcohol or a history of alcohol abuse was involved in some of the fatal and nonfatal reports. Nonfatal overdoses in pediatric patients ages 1 to 4 years old of 100 mg/kg for one to two doses has been reported.

12. The **OVERDOSAGE/Acute Toxicity/Signs and Symptoms/Rifampin** subsection has been revised as follows

### **Rifampin**

Nausea, vomiting, abdominal pain, pruritus, headache, and increasing lethargy will probably occur within a short time after rifampin overdose; 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 overdose; 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.

Facial or periorbital edema has also been reported in pediatric patients. Hypotension, sinus tachycardia, ventricular arrhythmias, seizures and cardiac arrest were reported in some fatal cases.

13. The **OVERDOSAGE/Treatment** subsection has been revised as follows:

### **Treatment**

The airway should be secured and adequate respiratory exchange should be established in cases of overdose with RIFATER. Only then should gastric emptying (lavage-aspiration) be attempted; this may be difficult because of seizures.

Obtain blood samples for immediate determination of gases, electrolytes, BUN, glucose, etc; type and cross-match blood in preparation for possible hemodialysis.

Gastric lavage within the first 2 to 3 hours after ingestion is advised, but it should not be attempted until convulsions are under control. To treat convulsions, administer IV diazepam or short-acting barbiturates, and IV pyridoxine (usually 1 mg/1 mg isoniazid ingested). Following evacuation of 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.

RAPID CONTROL OF METABOLIC ACIDOSIS IS FUNDAMENTAL TO MANAGEMENT. Give IV sodium bicarbonate at once and repeat as needed, adjusting subsequent dosage on the basis of laboratory findings (ie, serum sodium, pH, etc).

Forced osmotic diuresis must be started early and should be continued for some hours after clinical improvement to hasten renal clearance of drug and help prevent relapse; monitor fluid intake and output.

Hemodialysis is advised. Bile drainage may be indicated in presence of serious impairment of hepatic function lasting more than 24-48 hours. Under these circumstances and for severe cases, extracorporeal hemodialysis may be required; if this is not available, peritoneal dialysis can be used along with forced diuresis.

Along with measures based on initial and repeated determination of blood gases and other laboratory tests as needed, utilize meticulous respiratory and other intensive care to protect against hypoxia, hypotension, aspiration pneumonitis, etc.

Untreated or inadequately treated cases of gross isoniazid overdosage can terminate fatally, but good response has been reported in most patients brought under adequate treatment within the first few hours after drug ingestion.

14. The **DOSAGE and ADMINISTRATION** section has been revised relocating information on **Adult** and **Pediatric Patient** information in two separate sections as follows:

~~**Adults:** Patients should be given the following single daily dose of RIFATER either 1 hour before or 2 hours after a meal with a full glass of water.~~

~~Patients weighing  $\leq 44$  kg — 4 tablets~~

~~Patients weighing between 45-54 kg — 5 tablets~~

~~Patients weighing  $\geq 55$  kg — 6 tablets~~

~~**Pediatric Patients:** The ratio of the drugs in RIFATER may not be appropriate in pediatric patients under the age of 15 (eg, higher mg/kg doses of isoniazid are usually given in pediatric patients than adults).~~

RIFATER is recommended in the initial phase of short-course therapy which is usually continued for 2 months. The Advisory Council for the Elimination of Tuberculosis, the American Thoracic Society, and the Centers for Disease Control and Prevention recommend that either streptomycin or ethambutol be added as a fourth drug in a regimen containing isoniazid (INH), rifampin and pyrazinamide for initial treatment of tuberculosis unless the likelihood of INH or rifampin resistance is very low. The need for a fourth drug should be reassessed when the results of susceptibility testing are known. If community rates of INH resistance are currently less than 4%, an initial treatment regimen with less than four drugs may be considered.

Following the initial phase, treatment should be continued with rifampin and isoniazid (eg, RIFAMATE<sup>®</sup>) for at least 4 months. Treatment should be continued for longer if the patient is still sputum or culture positive, if resistant organisms are present, or if the patient is HIV positive.

Concomitant administration of pyridoxine (B<sub>6</sub>) is recommended in the malnourished, in those predisposed to neuropathy (eg, alcoholics and diabetics), and in adolescents.

See CLINICAL PHARMACOLOGY, General, for dosing information in patients with renal failure.

### **Adults**

Patients should be given the following single daily dose of RIFATER either 1 hour before or 2 hours after a meal with a full glass of water.

Patients weighing <44 kg – 4 tablets

Patients weighing between 45-54 kg – 5 tablets

Patients weighing ≥55 kg – 6 tablets

### **Pediatric Patients**

The ratio of the drugs in RIFATER may not be appropriate in pediatric patients under the age of 15 (eg, higher mg/kg doses of isoniazid are usually given in pediatric patients than adults).

We also note that your proposed labeling contains numerous editorial corrections, including a revision to the Reference section, that 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 Hyun J. Son, Pharm.D., 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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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OZLEM A BELEN  
11/12/2010