HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PRIFTIN® safely and effectively. See full prescribing information for PRIFTIN.

PRIFTIN® (rifapentine) Tablets
Initial U.S. Approval: 1998

INDICATIONS AND USAGE

• PRIFTIN is a rifamycin antimycobacterial drug indicated in patients 12 years of age and older for the treatment of active pulmonary tuberculosis (TB) caused by Mycobacterium tuberculosis in combination with one or more antituberculosis (anti-TB) drugs to which the isolate is susceptible. (1.1)

• PRIFTIN is indicated for the treatment of latent tuberculosis infection (LTBI) caused by M. tuberculosis in combination with isoniazid in patients 2 years of age and older at high risk of progression to TB disease. (1.2)

See Limitations of Use. (1.1, 1.2)

Dosage and Administration

Active pulmonary tuberculosis: PRIFTIN should be used in regimens consisting of an initial 2 month phase followed by a 4 month continuation phase. (2.1)

Initial phase (2 Months): 600 mg twice weekly for two months as directly observed therapy (DOT), with no less than 72 hours between doses, in combination with other antituberculosis drugs. (2.1)

Continuation phase (4 Months): 600 mg once weekly for 4 months as directly observed therapy with isoniazid or another appropriate antituberculosis agent. (2.1)

Latent tuberculosis infection: PRIFTIN should be administered in combination with isoniazid once weekly for 12 weeks as directly observed therapy. (2.1)

Adults and children ≥12 years: PRIFTIN (based on weight, see table below) and isoniazid 15 mg/kg (900 mg maximum) per day.

Children 2 to 11 years: PRIFTIN (based on weight, see table below) and isoniazid 25 mg/kg (900 mg maximum) per day.

Children 2 to 11 years: PRIFTIN should be administered in combination with isoniazid and rifampicin 15 mg/kg (900 mg maximum) per day.

For Latent Tuberculosis Infection, the maximum recommended dose of PRIFTIN is 900 mg once weekly for 12 weeks.

Dosage Forms and Strengths

PRIFTIN® Tablets

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For patients who cannot swallow tablets, the tablets may be crushed and added to a small amount of
water. PRIFTIN should not be used once weekly in the continuation phase regimen in combination
with isoniazid (INH) in HIV-infected patients with active pulmonary tuberculosis because of a higher rate of
failure and/or relapse with rifampin (RIF)-resistant organisms [see Warnings and Precautions (5.3) and
Clinical Studies (14.1)].

Limitations of Use

PRIFTIN should be administered at a dose of 600 mg twice weekly for 12 weeks as directly observed
therapy. Discontinue PRIFTIN if evidence of liver injury occurs. Monitor patients receiving PRIFTIN therapy for
signs and/or symptoms of hypersensitivity reactions. If these symptoms occur, administer supportive measures and discontinue PRIFTIN.

5.3 Relapse in the Treatment of Active Pulmonary Tuberculosis

PRIFTIN has not been evaluated as part of the initial phase treatment regimen in HIV-infected patients with
active pulmonary TB. Do not use PRIFTIN as a once-weekly continuation phase regimen in HIV-infected patients with active pulmonary tuberculosis because of a higher rate of failure and/or relapse with rifampin-resistant organisms [see Clinical Studies (14.1)].

Higher relapse rates may occur in patients with cavitary pulmonary lesions and/or positive sputum cultures after the initial phase of active tuberculosis treatment and in patients with evidence of blaleral pulmonary disease. Monitor for signs and symptoms of TB relapse in these patients [see Clinical Studies (14.2)].

5.4 Drug Interactions

Rifampine is an inducer of CYP450 enzymes. Concomitant use of rifampine with other drugs metabolized by these enzymes, such as protease inhibitors, can result in decreased effects of these drugs. See Table 3 for a list of drugs that should not be used with PRIFTIN.

5.5 Discoloration of Body Fluids

PRIFTIN may produce a red-orange discoloration of body tissues and/or fluids (e.g., skin, teeth, tongue, urine, feces, saliva, sputum, tears, sweat, and cerebrospinal fluid). Contact lenses or dentures may become permanently stained.

6 ADVERSE REACTIONS

The following serious and otherwise important adverse drug reactions are discussed in greater detail in other sections of labeling:

- Hepatotoxicity [see Warnings and Precautions (5.1)]
- Hypersensitivity [see Contraindications (4.1) and Warnings and Precautions (5.2)]
- Discoloration of Body Fluids [see Warnings and Precautions (5.5)]
- Clostridium Difficile-Associated Diarrhea [see Warnings and Precautions (5.6)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Active Pulmonary Tuberculosis

PRIFTIN was studied in a randomized, open label, active-controlled trial of HIV-negative patients with active pulmonary tuberculosis. The population consisted primarily of male subjects with a mean age of 37 ± 11 years. In the initial 2 month phase of treatment, 381 patients received PRIFTIN 600 mg twice weekly in combination with daily isoniazid, pyrazinamide, and ethambutol. Thirty-six patients (9.5%) experienced a relapse. The relapse rate was significantly lower compared to a control group of 361 patients who received rifampin in combination with isoniazid, pyrazinamide and ethambutol all administered daily. Ethambutol was discontinued when drug susceptibility testing was known. During the 4 month continuation phase, 317 patients in the PRIFTIN group continued to receive PRIFTIN 600 mg dosed once weekly with isoniazid and 304 patients in the rifampin group received twice weekly rifampin and isoniazid. Both treatment groups received pyridoxine (Vitamin B6) over the 6 month treatment period.

Because PRIFTIN was administered as part of a combination regimen, the adverse reaction profile reflects the entire regimen.

Twenty-two deaths occurred in the study, eleven in the rifampin combination therapy group and eleven in the PRIFTIN combination therapy group. 18/361 (5%) rifampin combination therapy patients discontinued the study due to an adverse reaction compared to 11/361 (3%) PRIFTIN combination therapy patients. Three patients (two rifampin combination therapy patients and one PRIFTIN combination therapy patient) were discontinued in the initial phase due to hepatotoxicity. Concomitant medications for all three patients included isoniazid, pyrazinamide, ethambutol, and pyridoxine. All three recovered without sequelae.

Five patients had adverse reactions associated with PRIFTIN overdose. These reactions included hematuria, neutropenia, hyperglycemia, ALT increased, hyperuricemia, purpuria, and arthritis.

Table 2 presents selected treatment-emergent adverse reactions associated with the treatment regimen which occurred in at least 1% of patients during treatment and post treatment through the first three months of follow-up.

<table>
<thead>
<tr>
<th>Weight range</th>
<th>PRIFTIN dose</th>
<th>Number of PRIFTIN tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–14 kg</td>
<td>300 mg</td>
<td>2</td>
</tr>
<tr>
<td>14.1–25 kg</td>
<td>450 mg</td>
<td>3</td>
</tr>
<tr>
<td>25.1–32 kg</td>
<td>600 mg</td>
<td>4</td>
</tr>
<tr>
<td>32.1–50 kg</td>
<td>750 mg</td>
<td>5</td>
</tr>
<tr>
<td>&gt;50 kg</td>
<td>900 mg</td>
<td>6</td>
</tr>
</tbody>
</table>
Table 2: Selected Treatment Emergent Adverse Reactions During Treatment of Active Pulmonary Tuberculosis and Through Three Months Follow-up

<table>
<thead>
<tr>
<th>System Organ Class Preferred Term</th>
<th>Initial Phase 1</th>
<th>Continuation Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLOOD AND LYMPHATICS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>41 (11.4)</td>
<td>41 (11.4)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>38 (10.5)</td>
<td>37 (10.2)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22 (6.1)</td>
<td>21 (5.8)</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>6 (1.7)</td>
<td>13 (3.6)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>20 (5.5)</td>
<td>13 (3.6)</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>6 (1.7)</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>4 (1.1)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Nonprotein Nitrogen Increased</td>
<td>4 (1.1)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td><strong>EYE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>8 (2.2)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6 (1.7)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (1.7)</td>
<td>14 (3.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (1.9)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (1.4)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td><strong>GENERAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>15 (4.2)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>3 (0.8)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Fever</td>
<td>5 (1.4)</td>
<td>7 (1.9)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>14 (3.9)</td>
<td>18 (5)</td>
</tr>
<tr>
<td><strong>HEPATIC &amp; BILIARY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT Increased</td>
<td>18 (5)</td>
<td>23 (6.4)</td>
</tr>
<tr>
<td>AST Increased</td>
<td>15 (4.2)</td>
<td>18 (5)</td>
</tr>
<tr>
<td><strong>MUSCULOSKELETAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>13 (3.6)</td>
<td>13 (3.6)</td>
</tr>
<tr>
<td><strong>NEUROLOGIC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>11 (3)</td>
<td>13 (3.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (1.4)</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td><strong>RESPIRATORY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>27 (7.5)</td>
<td>20 (5.5)</td>
</tr>
<tr>
<td>Coughing</td>
<td>21 (5.8)</td>
<td>8 (2.2)</td>
</tr>
<tr>
<td><strong>SKIN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>15 (4.2)</td>
<td>26 (7.2)</td>
</tr>
<tr>
<td>Sweating Increased</td>
<td>19 (5.3)</td>
<td>18 (5)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10 (2.8)</td>
<td>16 (4.4)</td>
</tr>
<tr>
<td>Rash Maculopapular</td>
<td>6 (1.7)</td>
<td>3 (0.8)</td>
</tr>
</tbody>
</table>

Initial phase consisted of therapy with either PRIFTIN twice weekly or rifampin daily combined with daily isoniazid, pyrazinamide, and ethambutol for 60 days.

†Continuation phase consisted of therapy with either PRIFTIN once weekly or rifampin twice weekly combined with daily isoniazid for 120 days.

The following selected treatment-emergent adverse reactions were reported in less than 1% of the PRIFTIN combination therapy patients during treatment and post treatment through the first three months of follow-up:

Blood and Lymphatics: lymphocytosis, hematoma, purpura, thrombosis.
Cardiovascular: syncope, tachycardia, palpitation, orthostatic hypotension, pericarditis.
Metabolic & Nutritional: BUN increased, alkaline phosphatase increased.
Gastrointestinal: gastritis, esophagitis, pancreatitis, salivary gland enlargement.
General: asthenia, facial edema.
Hepatobiliary: bilirubinemia, hepatomegaly, jaundice.
Infectious Disease: infection fungal.
Musculoskeletal: myalgia, myositis.
Neurologic: somnolence, dysphonia.
Pregnancy, Puerperium and Perinatal Conditions: abortion.
Psychiatric: anxiety, confusion.
Reproductive Disorders: vaginitis, vaginal hemorrhage, leukorrhea.
Respiratory: dyspnea, pneumonitis, pulmonary fibrosis, asthma, bronchospasm, laryngeal edema, laryngitis.
Skin: urticaria, skin discoloration.

In another randomized, open-label trial, 1075 HIV non-infected and infected patients with active pulmonary tuberculosis who had completed an initial 2 month phase of treatment with 4 drugs were randomly assigned to receive either PRIFTIN 600 mg and isoniazid once weekly or rifampin and isoniazid twice weekly for the 4 month continuation phase. 502 HIV non-infected and 36 HIV-infected patients were randomized to receive the PRIFTIN regimen and 502 HIV-noninfected and 35 HIV-infected patients were randomized to receive the rifampin regimen.

The death rate was 6.5% for the PRIFTIN combination regimen compared to 6.7% for the rifampin combination regimen.

**Table 3: Select Adverse Reactions Occurring in 0.5% or Greater of Patients in the Latent Tuberculosis Infection Main Study**

<table>
<thead>
<tr>
<th>System Organ Class Preferred Term</th>
<th>3RPT/NIH <em>(N=361)</em></th>
<th>9INH <em>(N=3759)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>161 (4)</td>
<td>18 (0.5)</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis</td>
<td>24 (0.6)</td>
<td>113 (3)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>26 (0.6)</td>
<td>17 (0.5)</td>
</tr>
</tbody>
</table>

*Includes events reported through 60 days after last dose of study drug.

**Pediatric Substudy**

Six hundred and ninety children 2 to 17 years of age received at least one dose of study drugs in the main study. An additional 342 children 2 to 17 years of age received at least one dose in the pediatric extension study (total of 1032 children; 539 received 3RPT/NIH and 493 received 9INH). No children in either treatment group developed hepatotoxicity. Using the same definition for rifamycin hypersensitivity reaction as in the main study, 7 (1.3%) of children in the 3RPT/NIH group experienced a rifamycin hypersensitivity reaction. Adverse reactions in children 2 to 17 years of age and 12 to 17 years of age were similar.

**HIV Substudy**

Two hundred HIV-infected patients with latent tuberculosis infection received at least one dose of study drugs in the main study. An additional 193 patients received at least one dose in the extension study (total of 393; 207 received 3RPT/NIH and 186 received 9INH). Compared to the HIV-negative patients enrolled in the main study, a higher proportion of HIV-infected patients in each treatment arm experienced a treatment emergent adverse reaction, including a higher incidence of hepatotoxicity. Two patients in the 3RPT/NIH arm and 11 patients in the 9INH arm experienced hepatotoxicity occurring in only one HIV-infected patient.

Eleven deaths occurred during the 33 month follow up period (6/207 in the 3RPT/NIH group and 5/186 in the 9INH group) including one death in the 9INH arm during the treatment emergent period. None of the reported deaths were considered related to treatment with study drugs or were attributed to tuberculosis disease.

Table 3 presents select adverse reactions that occurred during the treatment emergent period in the main study in LTBI patients treated with 3RPT/NIH or 9INH at a frequency greater than 0.5%.
Dosage adjustments of the drugs in Table 4 or of other drugs metabolized by cytochrome P450 3A4. Rifampin has been reported to accelerate the metabolism and may reduce the activity of the following enzyme activities by PRIFTIN occurred within 4 days after the first dose. Enzyme activities returned to baseline levels 14 days after discontinuing PRIFTIN.

7.2 Fixed Dose Combination of Efavirenz, Emtricitabine and Tenofovir
Once-weekly coadministration of 900 mg PRIFTIN with the antiretroviral fixed dose combination of efavirenz 600 mg, emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg in HIV-infected patients did not result in any substantial change in steady state exposures of efavirenz, emtricitabine, and tenofovir. No clinically significant change in CD4 cell counts or viral loads were noted [see Clinical Pharmacology (12.3)].

7.3 Hormonal Contraceptives
PRIFTIN may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to change to non-hormonal methods of birth control.

7.4 Cytochrome P450 3A4 and 2C8/9
Rifapentine is an inducer of CYP450 enzymes. Concomitant use of PRIFTIN with other drugs metabolized by these enzymes, such as protease inhibitors and certain reverse transcriptase inhibitors, may cause a significant decrease in plasma concentrations and loss of therapeutic effect of the protease inhibitor or reverse transcriptase inhibitor [see Warnings and Precautions (5.4) and Clinical Pharmacology (12.3)].

7.5 Other Interactions
The conversion of PRIFTIN to 25-desacetyl rifapentine is mediated by an esterase enzyme. There is minimal potential for PRIFTIN metabolism to be inhibited or induced by another drug, based upon the characteristics of the esterase enzymes. Since PRIFTIN is highly bound to albumin, drug displacement interactions may also occur [see Clinical Pharmacology (12.3)].

7.6 Interactions with Laboratory Tests
Therapeutic concentrations of rifapentine have been shown to inhibit standard microbiological assays for serum folate and Vitamin B12. Similar drug-laboratory interactions should be considered for PRIFTIN; thus, alternative assay methods should be considered.

8. USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C: Risk Summary
There are adequate and well controlled trials of PRIFTIN in pregnant women; however, there are limited pregnancy outcome data reported from women enrolled in clinical trials of various PRIFTIN treatment regimens for active tuberculosis and latent tuberculosis infection. The reported rate of spontaneous abortion following PRIFTIN exposure did not represent an increase over the background rate of spontaneous abortion reported in the general population. Further interpretation of these data is limited by the quality of clinical trial adverse event reporting. In animal reproduction and developmental toxicity studies, rifapentine produced fetal harm and was teratogenic at doses less than and similar to the recommended human dose. Because animal studies are not always predictive of human response, PRIFTIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations
Labor or Delivery
When administered during the last few weeks of pregnancy, rifampin, another rifamycin product, may increase the risk for maternal postpartum hemorrhage and bleeding in the exposed neonate. Monitor prothrombin time of pregnant women and neonates, who are exposed to PRIFTIN during the last few weeks of pregnancy. Treatment with Vitamin K may be indicated.

Human Data
Fourteen patients with active tuberculosis treated with multiple antituberculosis drugs including PRIFTIN became pregnant during clinical studies. Six delivered normal infants; four had first trimester spontaneous abortions (of these, one patient abused ethanol and another patient was HIV-infected); one had an elective abortion; and outcome was unknown in three patients. These data are, however, limited by the quality of reporting and confounded by comorbid medical conditions and multiple antituberculosis drug exposures.

In the trial that compared the safety and effectiveness of PRIFTIN in combination with isoniazid to isoniazid alone for the treatment of latent tuberculosis infection, a total of 45 (2.5%) women in the PRIFTIN/isoniazid arm and 71 (4.1%) women in the isoniazid arm became pregnant. Among the 46 total pregnancies in the PRIFTIN/isoniazid arm, there were 31 live births, six elective abortions, seven spontaneous abortions, and two unknown outcomes. Of the 31 live infants, 21 were reported healthy while in the other ten cases no further details were available. No congenital anomalies were reported. The rate of spontaneous abortion in the PRIFTIN/isoniazid arm (15%), and the rate of spontaneous abortion in the isoniazid arm (19%), did not represent an increase over the background rate of 15 to 20 percent reported in the general population. Further interpretation of these results is limited by the quality of adverse event reporting.

Animal Data
Animal studies in rats and rabbits revealed embryofetal toxicity in both species. Pregnant rats given oral rifapentine during organogenesis at 40 mg/kg/day (0.6 times the human dose of 600 mg based on body surface area), produced pups with cleft palates, right aortic arch, increased incidence of delayed ossification, and increased numbers of ribs. When rifapentine was administered to female rabbits late in gestation, at 20 mg/kg/day (0.3 times the human dose based on body surface area), pup weights and gestational survival (live pups born/pups born) were reduced compared to controls. Increased resections and post implantation loss, decreased mean fetal weights, increased numbers of stillborn pups, and slightly increased pup mortality during lactation were also noted. When pregnant rabbits received oral rifapentine at 10 mg/kg to 40 mg/kg (0.3 times to 1.3 times the human dose based on body surface area), major fetal malformations occurred including; ovarian agenesis, pes varus, arthria, microphthalmia and irregularities of the ossified facial tissues. At the higher dose, there were increases in post-implantation loss and the incidence of stillborn pups.

8.3 Nursing Mothers
It is not known whether PRIFTIN is present in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother [see Nonclinical Toxicology (13.1)]. Since PRIFTIN may produce a red-orange discoloration of body fluids, there is a potential for discoloration of breast milk. A slight increase in rat pup mortality was observed during lactation when dams were dosed late in gestation through lactation.

8.4 Pediatric Use
The safety and effectiveness of PRIFTIN in the treatment of active pulmonary tuberculosis has not been established in pediatric patients under the age of 12.

The safety and effectiveness of PRIFTIN in combination with isoniazid once-weekly regimen has been evaluated in pediatric patients (2–17 years of age) for the treatment of latent tuberculosis infection. In clinical studies, the safety profile in children was similar to that observed in adult patients [see Adverse Reactions (6.1) and Clinical Studies (14.2)].

In a pharmacokinetic study conducted in 2-year-old to 11-year-old pediatric patients with latent tuberculosis infection, PRIFTIN was administered once weekly based on weight (15 mg/kg to 30 mg/kg, up to a maximum of 800 mg). Exposures (AUC) in children 2 to 11 years old with latent tuberculosis infection were higher (average 31%) than those observed in adults receiving PRIFTIN 800 mg once weekly [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].
8.5 Geriatric Use
Clinical studies with PRIFTIN did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. In a pharmacokinetic study with PRIFTIN, no substantial differences in the pharmacokinetics of rifapentine and 25-desacetyl metabolite were observed in the elderly compared to younger adults [see Clinical Pharmacology (12.3)].

10 OVERDOSAGE
While there is no experience with the treatment of acute overdose with PRIFTIN, clinical experience with rifampicin suggests that gastric lavage to evacuate gastric contents (within a few hours of overdose), followed by institution of an activated charcoal slurry into the stomach, may help adsorb any remaining drug from the gastrointestinal tract.

Rifapentine and 25-desacetyl rifapentine are 97.7% and 93.2% plasma protein bound, respectively. Rifapentine and related compounds excreted in urine account for only 17% of the administered dose. Therefore, neither hemodialysis nor forced diuresis is expected to enhance the systemic elimination of unchanged rifapentine from the body of a patient with PRIFTIN overdose.

11 DESCRIPTION
PRIFTIN (rifapentine) for oral administration contains 150 mg of the active ingredient rifapentine per tablet.

The 150 mg tablets also contain, as inactive ingredients: calcium stearate, disodium EDTA, FD&C Blue No. 2 aluminum lake, hydroxypropyl cellulose, hypromellose USP, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, propylene glycol, sodium ascorbate, sodium lauryl sulfate, sodium starch glycolate, synthetic red iron oxide, and titanium dioxide.

Rifapentine is a rifamycin derivative antimicrobial and has a similar profile of microbiological activity to rifampin.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Rifapentine, a cyclopentyl rifamycin, is an antitymocellular agent [see Clinical Pharmacology, Microbiology (12.4)].

12.3 Pharmacokinetics
When oral doses of PRIFTIN were administered once daily or once every 72 hours to healthy volunteers for 10 days, single dose AUC ([0–24h]) of rifapentine was similar to its steady-state AUC ([0–24h]) or AUC ([0–12h]) values, suggesting no significant auto-induction effect on steady-state pharmacokinetics of rifapentine. Steady-state conditions were achieved by day 10 following daily administration of PRIFTIN 600 mg. No plasma accumulation of rifapentine and 25-desacetyl rifapentine (active metabolite) is expected after once weekly administration of PRIFTIN.

The pharmacokinetic parameters of rifapentine and 25-desacetyl rifapentine on day 10 following oral administration of 600 mg PRIFTIN every 72 hours to healthy volunteers are described in Table 5.

Table 5: Pharmacokinetics and Rifapentine and 25-Desacetyl Rifapentine in Healthy Volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rifapentine</th>
<th>25-Desacetyl Rifapentine</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(max) (µg/mL)</td>
<td>15.05 ± 4.62</td>
<td>6.26 ± 2.06</td>
</tr>
<tr>
<td>AUC ([0–24h]) (µg·h/mL)</td>
<td>319.54 ± 91.52</td>
<td>215.88 ± 65.96</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>13.19 ± 1.38</td>
<td>13.35 ± 2.67</td>
</tr>
<tr>
<td>T(max) (h)</td>
<td>4.83 ± 1.80</td>
<td>11.25 ± 2.73</td>
</tr>
<tr>
<td>Cl/F (L/h)</td>
<td>2.03 ± 0.60</td>
<td>--</td>
</tr>
</tbody>
</table>

The pharmacokinetic parameters of rifapentine and 25-desacetyl rifapentine following single-dose oral administration of 900 mg PRIFTIN in combination with 900 mg isoniazid in fed conditions are described in Table 6.

Table 6: Mean ± SD Pharmacokinetic Parameters of Rifapentine and 25-Desacetyl Rifapentine in Healthy Volunteers When PRIFTIN is Coadministered with Isoniazid Under Fed Conditions (N=16)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rifapentine</th>
<th>25-Desacetyl Rifapentine</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(max) (µg/mL)</td>
<td>25.8 ± 5.83</td>
<td>13.3 ± 4.83</td>
</tr>
<tr>
<td>AUC (µg·h/mL)</td>
<td>817 ± 128</td>
<td>601 ± 187</td>
</tr>
<tr>
<td>T(1/2) (h)</td>
<td>16.6 ± 5.02</td>
<td>17.5 ± 7.42</td>
</tr>
</tbody>
</table>

*Median (Min–Max). †Not Applicable.

Absorption
The absolute bioavailability of rifapentine has not been determined. The relative bioavailability (with an oral solution as a reference) of PRIFTIN after a single 600 mg dose to healthy adult volunteers was 70%. The maximum concentrations were achieved from 5 hours to 6 hours after administration of the 600 mg PRIFTIN dose.

The administration of PRIFTIN with a high fat meal increased rifapentine C(max) and AUC by 40% to 45% and 25% to 30% that observed when PRIFTIN was administered under fasting conditions.

The administration of PRIFTIN (900 mg single dose) and isoniazid (900 mg single dose) with a low fat, high carbohydrate breakfast, led to a 47% and 51% increase in rifapentine C(max) and AUC, respectively. In contrast, the ingestion of the same meal decreased isoniazid C(max) and AUC by 46% and 23%, respectively.

Distribution
In a population pharmacokinetic analysis in 351 tuberculosis patients who received 600 mg PRIFTIN in combination with isoniazid, pyrazinamide and ethambutol, the estimated apparent volume of distribution was 70.2 ± 9.1 L. In healthy volunteers, rifapentine and 25-desacetyl rifapentine were 97.3% and 85.2%, bound to plasma proteins, respectively. Rifapentine is mainly bound to albumin. Similar extent of protein binding was observed in healthy volunteers, asymptomatic HIV-infected subjects and heparically impaired subjects.

Metabolism/Excretion
Following a single 600 mg oral dose of radiolabeled rifapentine to healthy volunteers (n=4), 87% of the total radioactivity was recovered in the urine (17%) and feces (70%). Urine and feces represented 80% of the total radioactivity. The administration of rifapentine was excreted from the body within 7 days. Rifapentine was hydrolyzed by an esterase enzyme to form a microbiologically active 25-desacetyl rifapentine. Rifapentine and 25-desacetyl rifapentine accounted for 99% of the total radioactivity in plasma. Plasma AUC (0–24h) and C(max) values of 25-desacetyl rifapentine metabolite were one-half and one-third those of rifapentine, respectively. Based upon relative in vitro activities and AUC (0–24h) values, rifapentine and 25-desacetyl rifapentine potentially contributes 62% and 38% to the clinical activities against M. tuberculosis, respectively.

Specific Populations
Gender: In a population pharmacokinetics analysis of sparse blood samples obtained from 351 tuberculosis patients who received 600 mg PRIFTIN in combination with isoniazid, pyrazinamide and ethambutol, the estimated apparent oral clearance of PRIFTIN for males and females was 2.51 ± 0.14 L/h and 1.69 ± 0.41 L/h, respectively. The clinical significance of the difference in the estimated apparent oral clearance is not known.

Elderly: Following oral administration of a single 600 mg dose of PRIFTIN to elderly (65 years and older) healthy volunteers (n=14), the pharmacokinetics of rifapentine and 25-desacetyl metabolite were similar to that observed for young (18 to 45 years) healthy male volunteers (n=20).

Pediatric: In a pharmacokinetic study in pediatric patients (age 2 to 12 years), a single oral dose of 150 mg PRIFTIN was administered to those weighing less than 30 kg (n=11) and a single oral dose of 300 mg was administered to those weighing greater than 30 kg (n=12). The mean estimates of AUC and C(max) were approximately 30% to 50% lower in these pediatric patients than those observed in healthy adult patients administered single oral doses of 600 mg and 900 mg.

A study compared the pharmacokinetics of rifapentine in pediatric patients (age 2 years to 11 years) with latent tuberculosis infection (n=80) receiving PRIFTIN once weekly based on weight (15–30 mg/kg, up to a maximum of 900 mg, see Table 1) to that of adults (n=77) receiving PRIFTIN 900 mg once weekly. Children who could not swallow whole tablets were administered crushed tablets mixed in soft food. Overall, the geometric mean AUC of rifapentine in this age group was 21% higher compared to adult patients receiving 900 mg PRIFTIN once weekly (720 versus 551 mcg·h/mL). The geometric mean AUC of rifapentine was 60% higher in children administered whole tablets (884 versus 551 mcg·h/mL) and 19% higher in children administered crushed tablets (606 versus 551 mcg·h/mL), as compared to exposures in adults. Pediatric patients administered crushed PRIFTIN tablets had 26% lower rifapentine exposures compared to those pediatric patients who were given whole tablets.

Population pharmacokinetic analysis showed that rifapentine clearance adjusted to body weight decreased with increasing age of pediatric patients (2–18 years). In another pharmacokinetics study of PRIFTIN in healthy adolescents (age 12 to 15 years), 600 mg PRIFTIN was administered to those weighing ≥45 kg (n=10) and 450 mg was administered to those weighing less than 45 kg (n=2). The pharmacokinetics of rifapentine was similar to those observed in healthy adults.

Renal Impaired Patients: The pharmacokinetics of rifapentine has not been evaluated in renal impaired patients. Although only about 17% of an administered dose is excreted via the kidneys, the clinical significance of impaired renal function on the disposition of rifapentine and its 25-desacetyl metabolite is not known.

Hepatic Impaired Patients: Following oral administration of a single 600 mg dose of PRIFTIN to mildly to severe hepatic impaired patients (n=15), the pharmacokinetics of rifapentine and 25-desacetyl metabolite were similar in patients with various degrees of hepatic impairment and to that observed in another study for healthy volunteers (n=12).

Asymptomatic HIV-Infected Volunteers: Following oral administration of a single 600 mg dose of PRIFTIN to asymptomatic HIV-infected volunteers (n=15) under fasting conditions, mean C(max) and AUC (0–24h) of rifapentine were lower (20%–32%) than that observed in other studies in healthy volunteers (n=55). In a cross-study comparison, mean C(max) and AUC values of the 25-desacetyl rifapentine, when compared to healthy volunteers were higher (8%–21%) in one study (n=28), but lower (15%–16%) in another study (n=28). The clinical significance of this observation is not known. Food (850 total calories: 33 g protein, 55 g fat, and 58 g carbohydrate) increases the mean AUC and C(max) of rifapentine observed under fasting conditions in asymptomatic HIV-infected volunteers by about 51% and 33%, respectively.
Drug-Drug Interactions

Mutants in an otherwise susceptible population of in vitro of treatment, 361 patients received PRIFTIN 600 mg twice a week in combination with daily isoniazid, 60%) or multiracial (approximately 31%) patients. Treatment groups were comparable for age and sex, and consisted primarily of male subjects with a mean age of 37 ± 11 years. In the initial 2-month phase of treatment, 361 patients received PRIFTIN 600 mg twice a week in combination with daily isoniazid, pyrazinamide, and ethambutol and 361 subjects received rifampin 600 mg in combination with isoniazid, pyrazinamide and ethambutol all administered daily. The doses of the companion drugs were the same in both treatment arms during the initial phase: isoniazid 300 mg, pyrazinamide 2000 mg, and ethambutol 1200 mg. For patients weighing less than 50 kg, the doses of rifampin (450 mg), pyrazinamide (1500 mg) and ethambutol (800 mg) were reduced. Ethambutol was discontinued when isoniazid and rifampin susceptibility testing results were confirmed. During the 4 month continuation phase, 317 patients in the PRIFTIN group continued to receive PRIFTIN 600 mg dosed once weekly with isoniazid 300 mg and 304 patients in the rifampin group received twice weekly rifampin and isoniazid 900 mg. For patients weighing less than 50 kg, the doses of rifampin (450 mg) and isoniazid (600 mg) were reduced. Both treatment groups received pyridoxine (Vitamin B6) over the 6 month treatment period. Treatment was directly observed. 65/361 (18%) of patients in the PRIFTIN group and 34/361 (9%) in the rifampin group received overdoses of one or more of the administered study medications during the initial or continuation phase of treatment. Seven of these patients had adverse reactions reported with the overdose (5 in the PRIFTIN group and 2 in the rifampin group).

Table 8: Clinical Outcome in HIV Negative Patients with Active Pulmonary Tuberculosis

<table>
<thead>
<tr>
<th></th>
<th>PRIFTIN Combination Treatment % and (n/N)</th>
<th>Rifampin Combination Treatment % and (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status at End of 6 months of Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Converted</td>
<td>87% (248/286)</td>
<td>80% (226/283)</td>
</tr>
<tr>
<td>Not Converted</td>
<td>1% (4/286)</td>
<td>3% (8/283)</td>
</tr>
<tr>
<td>Lost to Follow-up</td>
<td>12% (34/286)</td>
<td>17% (49/283)</td>
</tr>
<tr>
<td>Status Through 24 Month Follow-up*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsed</td>
<td>12% (29/248)</td>
<td>7% (15/226)</td>
</tr>
<tr>
<td>Relapsed Negative</td>
<td>57% (142/248)</td>
<td>64% (145/226)</td>
</tr>
<tr>
<td>Lost to Follow-up</td>
<td>31% (77/248)</td>
<td>29% (60/226)</td>
</tr>
</tbody>
</table>

*All data for patients with confirmed susceptible M. tuberculosis (PRIFTIN combination treatment, N=286; rifampin combination treatment, N=283).
†Twenty-two (22) deaths occurred during the study, 11 in each treatment group.

Risk of relapse was greater in the group treated with the PRIFTIN combination. Higher relapse rates were associated with a lower rate of compliance as well as a failure to convert sputum cultures at the end of the initial 2-month treatment phase. Relapse rates were also higher for males in both regimens. Relapse in the PRIFTIN group was not associated with development of monoresistance to rifampin. The second trial was randomized, open-label performed in 1075 HIV-negative and positive patients with active pulmonary tuberculosis. Patients with culture-positive, drug-susceptible pulmonary tuberculosis who had completed the initial 2-month phase of treatment with 4 drugs (rifampin, isoniazid, pyrazinamide, and either ethambutol or streptomycin) under direct observation were randomly assigned to receive either PRIFTIN 600 mg and isoniazid 15 mg/kg (max 900 mg) once weekly or rifampin 10 mg/kg (max 600 mg) and isoniazid 15 mg/kg (max 900 mg) twice weekly for the 4 month continuation phase. Study drugs were given under direct observation therapy in both groups. In the PRIFTIN group, 502 HIV-negative and 36 HIV-positive patients were randomized and in the rifampin group 502 HIV-negative and 35 HIV-positive patients were randomized to treatment. Treatment of HIV-infected patients was dropped when 4 of 26 patients in the PRIFTIN group combination regimen with isolates that were rifampin resistant.

Table 9 below contains assessments of sputum conversion at the end of treatment (6 months total; 2 months of initial and 4 months of randomized continuation treatment) and relapse rates at the end of follow-up (24 months) in all HIV-negative patients randomized to treatment. Positive culture was based on either sputum sample with ≥10 colonies on solid media OR at least 2 positive sputum samples on liquid or solid media. However, only one sputum sample was collected at each visit in a majority of patients.

Table 9: Clinical Outcome in HIV Negative Patients with Active Pulmonary Tuberculosis

<table>
<thead>
<tr>
<th></th>
<th>PRIFTIN Combination Treatment % and (n/N)</th>
<th>Rifampin Combination Treatment % and (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status at End of 4 Months Continuation Phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Response†</td>
<td>93.8% (47/502)</td>
<td>91% (45/502)</td>
</tr>
<tr>
<td>Not Converted</td>
<td>1% (5/502)</td>
<td>1.2% (6/502)</td>
</tr>
<tr>
<td>Did Not Complete Treatment†</td>
<td>4.2% (21/502)</td>
<td>7% (30/502)</td>
</tr>
<tr>
<td>Deaths</td>
<td>1% (5/502)</td>
<td>0.6% (3/502)</td>
</tr>
<tr>
<td>Status Through 24 Month Follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsed</td>
<td>8.7% (41/471)</td>
<td>4.8% (22/475)</td>
</tr>
<tr>
<td>Sputum Negative</td>
<td>79.4% (374/471)</td>
<td>80.1% (366/471)</td>
</tr>
<tr>
<td>Lost to Follow-up</td>
<td>7.9% (37/471)</td>
<td>9.8% (45/475)</td>
</tr>
<tr>
<td>Deaths</td>
<td>4% (19/471)</td>
<td>5.3% (24/475)</td>
</tr>
</tbody>
</table>

†Treatment response was defined as subjects who had two negative sputum cultures after 16 doses of rifampin and isoniazid or after 8 doses of PRIFTIN and isoniazid, and remained sputum negative through the end of continuation phase therapy.
‡Due to drug toxic effects, non-adherence, withdrawal of consent, receipt of non-study regimen, other.

12.4 Microbiology

Mechanism of Action

Rifapentine, a cyclopyrenyl rifamycin, inhibits DNA-dependent RNA polymerase in susceptible strains of Mycobacterium tuberculosis but does not affect mammalian cells at concentrations that are active against these bacteria. At therapeutically relevant concentrations, rifapentine inhibits RNA transcription by preventing the initiation of RNA chain formation. It forms a stable complex with bacterial DNA-dependent RNA polymerase, leading to repression of RNA synthesis and cell death. Rifapentine and its 25-desacytely metabolite accumulate in human monocyt-derived macrophages and are bactericidal to both intracellular and extracellular M. tuberculosis bacilli.

Mechanism of Resistance

The mechanism of resistance to rifapentine appears to be similar to that of rifampin. Bacterial resistance to rifapentine is caused by an alteration in the target site, the beta subunit of the DNA-dependent RNA polymerase, caused by a one-step mutation in the rpoB gene. The incidence of rifapentine resistant mutants in an otherwise susceptible population of M. tuberculosis strains is approximately one in 10^10 bacilli. Rifapentine resistance appears to be associated with monotherapy. Therefore, rifapentine should always be used in combination with other antituberculosis drugs.

Cross Resistance

M. tuberculosis organisms resistant to other rifamycins are likely to be resistant to rifapentine. A high level of cross-resistance between rifampin and rifapentine has been demonstrated with M. tuberculosis strains. Cross-resistance between rifapentine and non-rifamycin antitubercular agents has not been identified in clinical isolates.

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.
In HIV-negative patients, higher relapse rates were seen in patients with a positive sputum culture at 2 months (i.e., at the time of study randomization), cavitation on chest x-ray, and bilateral pulmonary involvement.

Sixty-one HIV-negative patients were assessed for relapse. The rates of relapse were 16.7% (5/30) in the PRIFTIN group and 9.7% (3/31) in the rifampin group. In HIV-positive patients, 4 of the 5 relapses in the PRIFTIN combination group involved M. tuberculosis strains with rifampin monoresistance. No relapse strain in the twice weekly rifampin/isoniazid group acquired drug resistance.

The death rate among all study participants did not differ between the two treatment groups.

14.2 Tuberculosis Infection

A multi-center, prospective, open-label, randomized, active-controlled trial compared the effectiveness of 12 weekly doses of PRIFTIN in combination with isoniazid (3RPT/INH) arm administered by directly observed therapy to 9 months of self-administered daily isoniazid (9INH) arm. The trial enrolled patients two years of age or older with positive tuberculin skin test and at high risk for progression to tuberculosis disease. Enrolled patients included those having close contact with a patient with active tuberculosis disease, recent (within two years) conversion to a positive tuberculin skin test, HIV-infection, or fibrosis on chest radiograph. PRIFTIN was dosed by weight, for a maximum of 900 mg weekly. Isoniazid mg/kg dose was determined by age, for a maximum of 900 mg weekly in the 3RPT/INH arm and 300 mg daily in the 9INH arm [see Dosage and Administration (2.2)].

The outcome measure was the development of active tuberculosis disease, defined as culture confirmed tuberculosis in adults and culture-confirmed or clinical tuberculosis in children less than 18 years of age, at 33 months after trial enrollment. Patients who were found after enrollment to be ineligible because they had active tuberculosis disease, were contacts of a source case with culture-negative or drug-resistant tuberculosis disease cases or no information regarding susceptibility of M. tuberculosis, and young children lacking a positive TST on initial and repeat testing were excluded from the analysis.

Active tuberculosis disease developed in 5 of 3074 randomized patients in the 3RPT/INH group (0.16%) versus 10 of 3074 patients in 9INH group (0.32%), for a difference in cumulative rates of 0.17%, 95% CI (-0.43, 0.09) (Table 10).

Table 10: Outcomes in Randomized Patients at 33 Months Post Enrollment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>3RPT/INH (n=3074)</th>
<th>9INH (n=3074)</th>
<th>Difference, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis (%)</td>
<td>5 (0.16)</td>
<td>10 (0.32)</td>
<td>-0.16 (-0.42, 0.01)</td>
</tr>
<tr>
<td>Cumulative TB Rate (%)</td>
<td>0.17</td>
<td>0.35</td>
<td>-0.17 (-0.43, 0.09)</td>
</tr>
<tr>
<td>Deaths</td>
<td>22 (0.72)</td>
<td>36 (1.14)</td>
<td>-0.42 (-0.91, 0.06)</td>
</tr>
<tr>
<td>Lost to Follow-Up</td>
<td>320 (10.41)</td>
<td>357 (11.61)</td>
<td>-1.20 (-2.77, -0.36)</td>
</tr>
</tbody>
</table>

Table: similar results were observed when all enrolled patients were included in the analysis. Rate in the 3RPT/INH group minus the rate in the 9INH group.

The proportion of patients completing treatment was 81.2% in the 3RPT/INH group and 68.3% in the 9INH group for a difference (3RPT/INH-9INH) of 12.8% 95% CI (10.7, 15.0).

In the 9INH treatment group, two of the thirteen culture-confirmed cases were found to be isoniazid-monoresistant. In the 3RPT/INH treatment group, one of the seven cases was rifampin resistant, isoniazid-susceptible M. bovis infection.

Pediatric Sub-study

Enrollment of children was extended after the overall target number of patients was attained in the main study. Data from both the main study and the extension were pooled resulting in an eligible population for analysis of 375 patients in the 3RPT/INH and 367 in the 9INH arm. One child in the 9INH group developed tuberculosis (1/367, cumulative rate 0.22%) versus zero tuberculosis cases in the 3RPT/INH group (0/375) at 33 months post enrollment. The proportion of patients completing treatment in the 3RPT/INH and the 9INH groups was 87.5% and 79.6% respectively for a difference of 7.9%, 95% CI (-0.43, 0.09) (Table 10).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

PRIFTIN is supplied as 150 mg round convex pink-orange coated tablets debossed “F” on one side of tablet packaged in aluminum formable foil blister strips. Carton of 24 tablets (3 strips of 8 tablets) NDC 0088-2102-24

Storage

Store at 25°C (77°F); excursions permitted 15–30°C (59–86°F) (see USP Controlled Room Temperature). Protect from excessive heat and humidity.

17 PATIENT COUNSELING INFORMATION

17.1 Treatment Adherence

Emphasize the importance of compliance with the full course of therapy, and the importance of not missing any doses of PRIFTIN or companion medications in the treatment of active pulmonary tuberculosis or the treatment of latent tuberculosis infection.

17.2 Hypersensitivity Reactions

Inform patients that PRIFTIN may cause hypersensitivity reactions. Signs and symptoms of this reaction may include fever, rash, itching, hypotension, urticaria, angioedema, bronchospasm, conjunctivitis, thrombocytopenia or neutropenia. Anaphylaxis may also occur [see Warnings and Precautions (5.2)]. Inform patients of signs and symptoms of hypersensitivity reactions and advise them to stop the medication and contact their healthcare provider if they experience any of these symptoms.

17.3 Hepatitis

Instruct patients to stop the medication and notify their physician promptly if they experience any of the following: fever, loss of appetite, malaise, nausea and vomiting, darkened urine, yellowish discoloration of the skin and eyes, and pain or swelling of the joints [see Warnings and Precautions (5.1)].

17.4 Drug Interactions

Rifapentine may increase the metabolism and decrease the activity of other drugs that are metabolized by the P450 3A4 and 2C89 pathways. Dosage adjustments of the coadministered drugs may be necessary. Advise patients to discuss with their physician any other medications they are taking before starting treatment with PRIFTIN [see Warnings and Precautions (5.4), Drug Interactions (7.1) and (7.4)]. Concomitant use of PRIFTIN with protease inhibitors or reverse transcriptase inhibitors may cause a significant decrease in plasma concentrations and loss of therapeutic effect of the protease inhibitor or reverse transcriptase inhibitor [see Warnings and Precautions (5.4) and Drug Interactions (7.4)]. Rifapentine may reduce the effectiveness of hormonal contraceptives. Advise patients using oral, transdermal patch, or other systemic hormonal contraceptives to change to non-hormonal methods of birth control [see Drug Interactions (7.3)].

17.5 Discoloration of Body Fluids

Inform the patient that PRIFTIN produces a reddish coloration of the urine, sweat, sputum, tears, and breast milk. Contact lenses or dentures may be permanently stained [see Warnings and Precautions (5.5)].

17.6 Administration with Food

Advise patients to take PRIFTIN with food.

17.7 Nursing Mothers

Advise nursing mothers that breastfeeding is not recommended with PRIFTIN use [see Use in Specific Populations (8.3)].

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Bridgewater, NJ 08807
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Medication Guide

PRIFTIN (rif prfi -tin) (rifapentine) Tablets

Read this Medication Guide before you start taking PRIFTIN and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about PRIFTIN?

PRIFTIN may cause serious side effects, including:

- Liver problems. PRIFTIN may cause serious liver problems. Your doctor may do a blood test to check your liver function before and while you take PRIFTIN. Stop taking PRIFTIN and call your doctor right away if you have any of the following signs and symptoms of liver problems:
  - nausea
  - stomach pain
  - tiredness
  - yellowing skin or whites of your eyes
  - vomiting
  - loss of appetite
  - dark urine

- Allergic reactions and flu-like symptoms. Allergic reactions and flu-like symptoms have happened in some people taking PRIFTIN. Signs and symptoms of an allergic reaction may include:
  - low blood pressure (hypotension)
  - rash
  - cough with wheezing
  - difficulty breathing
  - red eyes (conjunctivitis)
  - lower blood platelet levels

Signs and symptoms of a flu-like reaction may include:
  - weakness
  - headache
  - aches
  - chest pain
  - fast heartbeat
  - muscle pain
  - fever
  - rash
  - dizziness
  - cough
What is PRIFTIN?
PRIFTIN is a prescription medicine used with other anti-
tuberculosis (TB) medicines to:
• treat active tuberculosis disease of the lung in people age 12
  years and older.
• prevent progression of inactive (latent) tuberculosis infection to
  active tuberculosis disease in people age 2 years and older.
PRIFTIN should not be used:
• alone to treat people with active or latent TB
• in people with active TB who had taken the medicines rifampin
  or isoniazid in the past and did not respond (resistant)
• in people who had been exposed to patients with TB that
  cannot be treated with isoniazid or rifampin
PRIFTIN is safe and effective in children older than 2 years of age
who have inactive (latent TB), but it is not known if PRIFTIN is
safe and effective for use in the treatment of active TB in children
under 12 years of age.

Who should not take PRIFTIN?
• Do not take PRIFTIN if you are allergic to a group of
  medicines called rifamycins.

What should I tell my doctor before taking PRIFTIN?
Before you take PRIFTIN, tell your doctor if you:
• have active TB disease
• know that you have TB that is resistant to treatment with some
  medicines
• have HIV infection or taking medicines to treat HIV infection
• have liver problems
• have a condition called porphyria
• are pregnant or planning to become pregnant. It is not known
  if PRIFTIN will harm your unborn baby.
• are breastfeeding or plan to breastfeed. It is not known if
  PRIFTIN passes into your breast milk. You and your doctor
  should decide if you will take PRIFTIN or breastfeed.

Tell your doctor about all the medicines you take, including
prescription and over-the-counter medicines, vitamins, and herbal
supplements.

Using PRIFTIN with other medicines may affect each other
causing serious side effects. PRIFTIN may affect the way other
medicines work, and other medicines may affect how PRIFTIN
works. Especially tell your doctor if you take medicines to treat
HIV infection or oral contraceptives.

Ask your doctor or pharmacist for a list of these medicines if you
are not sure.

Know the medicines you take. Keep a list of them to show your
doctor or pharmacist when you get a new medicine.

How should I take PRIFTIN?
• Take PRIFTIN exactly as your doctor tells you to take it.
  It is important to take all of your PRIFTIN and your other
  TB medicines. Do not skip doses. Skipping doses may
  cause PRIFTIN to not work as well and may increase the
  chance that your TB will not be treatable by PRIFTIN or other
  medicines.
• Take PRIFTIN with food.
• If you cannot swallow PRIFTIN tablets whole, they can be
  crushed and mixed with small amount of semisolid food. Be
  sure to take all of the semisolid food with PRIFTIN in it right
  away.

What are possible side effects of PRIFTIN?
PRIFTIN may cause serious side effects, including:
• See “What is the most important information I should
  know about PRIFTIN?”
• Relapse of your TB symptoms. Active TB disease may
  return after improvement (relapse) in some people, especially
  people who do not take PRIFTIN exactly as their doctor tells
  them to. It is important that you take PRIFTIN exactly as your
  doctor tells you to. Your doctor should check you for worsening
  signs and symptoms of your TB while you take PRIFTIN.
• change in the normal color of your skin, mouth and body
  fluids. PRIFTIN may cause your skin, teeth, tongue, urine,
  feces, saliva, sputum, tears, sweat, and breast milk to turn a
  red-orange color. Contact lenses or dentures may become
  permanently stained.
• diarrhea. A type of diarrhea called Clostridium difficile-
  associated diarrhea (CDAD) may occur during or after taking
  antibiotics, including PRIFTIN. The severity of CDAD can
  range from mild diarrhea to severe diarrhea that may cause
  death (fatal colitis). Tell your doctor right away if you have
  diarrhea while you take or after you stop taking PRIFTIN.
• worsening of a condition called porphyria.

The most common side effects of PRIFTIN include change in
the color of body fluids to orange-red, allergic reactions and flu-like
symptoms, abnormalities in liver tests, decrease in white blood cell
and red blood cell count, decreased appetite, skin rash or itching,
and red eyes.

Tell your doctor if you have any side effect that bothers you or
that does not go away. These are not all the possible side effects
of PRIFTIN. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may
report side effects to FDA at 1-800-FDA-1088.

How should I store PRIFTIN?
• Store PRIFTIN at room temperature between 68°F to 77°F
  (20°C to 25°C).
• Keep PRIFTIN dry and away from heat.
• Keep PRIFTIN and all medicines out of reach of children.

General information about the safe and effective use of
PRIFTIN.

Medicines are sometimes prescribed for purposes other than those
listed in a Medication Guide. Do not use PRIFTIN for a condition
for which it was not prescribed. Do not give PRIFTIN to other
people, even if they have the same symptoms you have. It may
harm them.

This Medication Guide summarizes the most important information
about PRIFTIN. If you would like more information, talk with your
doctor. You can ask your doctor or pharmacist for information
about PRIFTIN that is written for healthcare professionals.

For more information, go to www.sanofi.us or call 1-800-633-1610,
and select option 1.

What are the ingredients in PRIFTIN?
Active ingredient: rifapentine
Inactive ingredients: calcium stearate, disodium EDTA, FD&C
Blue No. 2 aluminum lake, hydroxypropyl cellulose, hypromellose
USP, microcrystalline cellulose, polyethylene glycol, pregelatinized
starch, propylene glycol, sodium ascorbate, sodium lauryl sulfate,
Sodium starch glycolate, synthetic red iron oxide, and titanium
dioxide

Manufactured by: sanofi-aventis U.S. LLC, Bridgewater, NJ 08807

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