PRIFTIN® (rifampine) tablets, for oral use

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®.

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)

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. PRIFTIN® should be administered in combination with isoniazid once weekly for 12 weeks as directly observed therapy. (2.2)

Latent tuberculosis infection: PRIFTIN® should be administered in combination with isoniazid once weekly for 12 weeks as directly observed therapy. (2.2)

Children 2 to 11 years: PRIFTIN® (based on weight, see table below) and isoniazid 25 mg/kg (900 mg maximum). (2.2)

Adults and children ≥12 years: PRIFTIN® (based on weight, see table below) and isoniazid 15 mg/kg (900 mg maximum). (2.2)

Dosage and Administration


<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>

For Latent Tuberculosis Infection, the maximum recommended dose of PRIFTIN is 900 mg once weekly for 12 weeks. (2.2)

• Take with food. Tablets may be crushed and added to semi-solid food. (2.3)

WARNINGS AND PRECAUTIONS

• Hepatotoxicity: Monitor for symptoms of liver injury and discontinue PRIFTIN if signs or symptoms of liver injury occur. (5.1)

• Hypersensitivity: Discontinue PRIFTIN if signs or symptoms of hypersensitivity reaction occur. (5.2)

• Severe cutaneous adverse reactions: Discontinue PRIFTIN at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. (5.3)

• Relapse in the treatment of active pulmonary tuberculosis: Do not use as a once-weekly continuation phase regimen with isoniazid in HIV-infected patients. Monitor for signs or symptoms of relapse in patients with cavitary lesions or bilateral disease. (5.4, 14.1)

• Drug Interactions: May interact with drugs metabolized by CYP450. (5.5, 7.1, 7.4)

• Discoloration of body fluids: May permanently stain contact lenses or dentures red-orange. (5.6)

• Oesophagitis difficile-associated diarrhea: Evaluate if diarrhea occurs. (5.7)

• Porphyria: Avoid use in patients with porphyria. (5.8)

ADVERSE REACTIONS

The most common adverse reactions with regimen for active pulmonary tuberculosis (3% and greater) are anemia, lymphopenia, hemoptysis, neutropenia, cough, thrombocytopenia, increased sweating, increased ALT, increased AST, back pain, rash, anorexia, arthralgia, increased blood urea, and headache. The most common adverse reaction (3% and greater) with the regimen for latent tuberculosis infection is hypersensitivity reaction. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

• Pgp and Oatp1b1/3 inhibitors: May increase metabolism and decrease the activity of drugs metabolized by cytochrome P450 3A4 and 2C8/9. Dosage adjustments may be necessary if given concomitantly. (7.4)

• Hormonal Contraceptives: Use an effective non-hormonal method of contraception or add a barrier method of contraception during treatment with PRIFTIN. (7.3)

USE IN SPECIFIC POPULATIONS

• Pregnancy: Based on animal data, may cause fetal harm. (8.1)

• Lactation: Monitor infants exposed to PRIFTIN through breast milk for irritability, prolonged sweating, increased ALT, increased AST, back pain, rash, anorexia, arthralgia, increased blood urea, and headache. The most common adverse reaction (3% and greater) with the regimen for latent tuberculosis infection is hypersensitivity reaction. (6.1)

• Children: Safety and effectiveness in treating active pulmonary tuberculosis in children under the age of 12 years have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 06/2020
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Active Pulmonary Tuberculosis

PRIFTIN® (rifapentine) is indicated in adults and children 12 years and older for the treatment of active pulmonary tuberculosis (TB) caused by Mycobacterium tuberculosis. PRIFTIN must always be used in combination with one or more antituberculosis (anti-TB) drugs to which the isolate is susceptible [see Dosage and Administration (2.1) and Clinical Studies (14.1)].

Limitations of Use

Do not use PRIFTIN monotherapy in either the initial or the continuation phases of active antituberculosis treatment.

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 (rifampicin)-resistant organisms [see Warnings and Precautions (5.4) and Clinical Studies (14.1)].

PRIFTIN has not been studied as part of the initial phase treatment regimen in HIV-infected patients with active pulmonary tuberculosis.

1.2 Latent Tuberculosis Infection

PRIFTIN is indicated in adults and children 2 years and older for the treatment of latent tuberculosis infection caused by Mycobacterium tuberculosis in patients at high risk of progression to tuberculosis disease (including those in close contact with active tuberculosis patients, recent conversion to a positive tuberculin skin test, HIV-infected patients, or those with pulmonary fibrosis on radiograph) [see Clinical Studies (14.2)].

Limitations of Use

Active tuberculosis disease should be ruled out before initiating treatment for latent tuberculosis infection.

PRIFTIN must always be used in combination with isoniazid as a 12-week once-weekly regimen for the treatment of latent tuberculosis infection [see Dosage and Administration (2.2) and Clinical Studies (14.2)].

• PRIFTIN in combination with isoniazid is not recommended for individuals presumed to be exposed to rifampin-resistant or isoniazid-resistant M. tuberculosis.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Active Pulmonary Tuberculosis

PRIFTIN is only recommended for the treatment of active pulmonary tuberculosis caused by drug-susceptible organisms as part of regimens consisting of a 2-month initial phase followed by a 4-month continuation phase.

PRIFTIN should not be used in the treatment of active pulmonary tuberculosis caused by rifampin-resistant strains.

Initial phase (2 Months): PRIFTIN should be administered at a dose of 600 mg twice weekly for two months as directly observed therapy (DOT), with an interval of no less than 3 consecutive days (72 hours) between doses, in combination with other antituberculosis drugs as part of an appropriate regimen which includes daily companion drugs such as isoniazid (INH), ethambutol (EMB) and pyrazinamide (PZA).

Continuation phase (4 Months): Following the initial phase (2 months), continuation phase (4 months) treatment consists of PRIFTIN 600 mg once weekly for 4 months in combination with isoniazid or another appropriate antituberculosis agent for susceptible organisms administered as directly observed therapy.

2.2 Dosage in Latent Tuberculosis Infection

PRIFTIN should be administered once weekly in combination with isoniazid for 12 weeks as directly observed therapy.

Adults and children 12 years and older: The recommended dose of PRIFTIN should be determined based on weight of the patient up to a maximum of 900 mg once weekly (see Table 1). The recommended dose of isoniazid is 15 mg/kg (rounded to the nearest 50 mg or 100 mg) up to a maximum of 900 mg once weekly for 12 weeks.

Children 2 to 11 years: The recommended dose of PRIFTIN should be determined based on weight of the patient up to a maximum of 900 mg once weekly (see Table 1). The recommended dose of isoniazid is 25 mg/kg (rounded to the nearest 50 mg or 100 mg) up to a maximum of 900 mg once weekly for 12 weeks.

2.3 Administration

Take PRIFTIN with meals. Administration of PRIFTIN with a meal increases oral bioavailability and may reduce the incidence of gastrointestinal upset, nausea, and/or vomiting [see Clinical Pharmacology (12.3)].

For patients who cannot swallow tablets, the tablets may be crushed and added to a small amount of semi-solid food, all of which should be consumed immediately [see Clinical Pharmacology (12.3)].

3 DOSAGE FORMS AND STRENGTHS

PRIFTIN is supplied as 150 mg round normal convex dark-pink film-coated tablets debossed “F” on one side of tablet.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

PRIFTIN is contraindicated in patients with a history of hypersensitivity to rifamycins.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Elevations of liver transaminases may occur in patients receiving PRIFTIN [see Adverse Reactions (6.1)]. Patients on PRIFTIN should be monitored for symptoms of liver injury. Patients with abnormal liver tests and/or liver disease or patients initiating treatment for active pulmonary tuberculosis should only be given PRIFTIN in cases of necessity and under strict medical supervision. In such patients, obtain serum transaminase levels prior to therapy and every 2 to 4 weeks while on therapy. Discontinue PRIFTIN if evidence of liver injury occurs.

5.2 Hypersensitivity and Related Reactions

Hypersensitivity reactions may occur in patients receiving PRIFTIN. Signs and symptoms of these reactions may include hypotension, urticaria, angioedema, acute bronchospasm, conjunctivitis, thrombocytopenia, neutropenia or flu-like syndrome (weakness, fatigue, muscle pain, nausea, vomiting, headache, fever, chills, ache, rash, itching, sweats, dizziness, shortness of breath, chest pain, cough, syncope, palpitations). There have been reports of anaphylaxis [see Patient Counseling Information (17)].

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 Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been reported in association with the use of rifapentine (PRIFTIN) treatment regimens in patients with active and latent tuberculosis. Discontinue PRIFTIN at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity [see Patient Counseling Information (17)].

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 bilateral pulmonary disease. Monitor for signs and symptoms of TB relapse in these patients [see Clinical Studies (14.1)].

Poor adherence to therapy is associated with high relapse rate. Emphasize the importance of compliance with therapy [see Patient Counseling Information (17)].

5.5 Drug Interactions

Rifapentine is an inducer of CYP450 enzymes. Concomitant use of rifapentine with other drugs metabolized by these enzymes, such as protease inhibitors, certain reverse transcriptase inhibitors, and hormonal contraception may cause a significant decrease in plasma concentrations and loss of therapeutic effect [see Drug Interactions (7.1, 7.2, 7.3, 7.4) and Clinical Pharmacology (12.3)].

5.6 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, sperm, tears, sweat, and cerebrospinal fluid). Contact lenses or dentures may become permanently stained.

5.7 Clostridioides Difficile-Associated Diarrhea

Clostridioides difficile-associated diarrhea (CDAD) has been reported with the use of nearly all systemic antibacterial agents, including PRIFTIN, with severity ranging from mild diarrhea to fatal colitis.

Treatment with antibacterial agents can alter the normal flora of the colon and may permit overgrowth of clostridia. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require surgical evaluation as clinically indicated.

5.8 Porphyria

Porphyria has been reported in patients receiving rifampin, attributed to induction of delta amino levulinic acid synthetase. Because PRIFTIN may have similar enzyme induction properties, avoid the use of PRIFTIN in patients with porphyria.

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)]
• Severe Cutaneous Adverse Reactions [see Warnings and Precautions (5.3)]

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Table 1: Weight Based Dose of PRIFTIN in the Treatment of Latent Tuberculosis Infection

<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>
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<td>4</td>
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<td>750 mg</td>
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</tr>
<tr>
<td>&gt;50 kg</td>
<td>900 mg</td>
<td>6</td>
</tr>
</tbody>
</table>

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Sections or subsections omitted from the full prescribing information are not listed.
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, 361 patients received PRIFTIN 600 mg twice a week in combination with daily isoniazid, pyrazinamide, and ethambutol and 361 subjects 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. Concurrent 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, pruritus, and arthritis.

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

Table 2: Selected Treatment Emergent Adverse Reactions during Treatment of Active Pulmonary Tuberculosis and through Three Months Follow-up (continued)

<table>
<thead>
<tr>
<th>System Organ Class Adverse Reaction</th>
<th>Initial Phase</th>
<th>Continuation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRIFTIN Combination (N=361)</td>
<td>Rifampin Combination (N=361)</td>
</tr>
<tr>
<td>Blood and lymphatics</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>Thrombocytosis</td>
<td>20 (5.5)</td>
<td>13 (3.6)</td>
</tr>
<tr>
<td>Thrombocytopenia</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>Eye</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>8 (2.2)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</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>General</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>Hepatic and biliary</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>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood urea increased</td>
<td>4 (1.1)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>13 (3.6)</td>
<td>13 (3.6)</td>
</tr>
</tbody>
</table>

+ Discoloration of Body Fluids [see Warnings and Precautions (5.6)]
+ Clostridium Difficile-Associated Diarrhea [see Warnings and Precautions (5.7)]
+ Porphyria [see Warnings and Precautions (5.8)]
(3%) patients. In the 9INH group, the most frequent treatment related adverse reaction resulting in treatment discontinuation was hepatotoxicity occurring in 72 (6%) patients. Seventy-nine deaths occurred, 31/4040, 0.77% in the 3RPT/INH group and 40/3759 (1.06%) in the 9INH group during the 33-month study period. During the treatment emergent period, 11 deaths occurred, 4 in the 3RPT/INH group and 7 in the 9INH group. None of the reported deaths were considered related to treatment with study drugs or were attributed to tuberculosis disease.

Table 3 presents adverse reactions that occurred during the treatment emergent period in the main study in LTBI patients treated with 3RPT/INH or 9INH at a frequency greater than 0.5%.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Reaction</th>
<th>3RPT/INH (N=4040) N (%)</th>
<th>9INH (N=3759) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity</td>
<td>161 (4)</td>
<td>18 (0.5)</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Hepatitis</td>
<td>24 (0.6)</td>
<td>113 (3)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>26 (0.6)</td>
<td>17 (0.5)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Skin reaction</td>
<td>31 (0.8)</td>
<td>21 (0.6)</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 1032 children; 539 received 3RPT/INH and 493 received 9INH). No children in either treatment arm developed hepatotoxicity. Using the same definition for rifampicin hypersensitivity reaction as in the main study, 7 (1.3%) of children in the 3RPT/INH group experienced a rifampicin hypersensitivity reaction. Adverse reactions in children 2 to 11 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 and an additional 193 patients received at least one dose in the extension study (total of 393; 207 received 3RPT/INH 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. Hepatotoxicity occurred in 3/207 (1.5%) patients in the 3RPT/INH arm and in 14/186 (7.5%) in the 9INH arm. Rifampicin hypersensitivity occurred in only one HIV-infected patient. Eleven deaths occurred during the 33-month follow-up period (6/207 in the 3RPT/INH 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 tuberculosis disease. Selected treatment-emergent adverse reactions reported during treatment and 60 days post treatment in less than 0.5% of the 3RPT/INH combination-therapy group in the main study are presented below by body system.

Eye Disorders: conjunctivitis.

Blood and Lymphatic System Disorders: leukopenia, anemia, lymphadenopathy, neutropenia.

Gastrointestinal Disorders: nausea, diarrhea, vomiting, abdominal pain, constipation, dry mouth, dyspepsia, esophageal irritation, gastritis, pancreatitis.

General Disorders and Administration Site Conditions: fatigue, pyrexia, asthenia, chest pain, chills, feeling jittery.

Infections and Infestations: pharyngitis, viral infection, vulvovaginal candidiasis.

Metabolism and Nutrition Disorders: hyperglycemia, gout, hyperkalemia, decreased appetite, hyperlipidemia.

Musculoskeletal and Connective Tissue Disorders: arthralgia, myalgia, back pain, rhabdomyolysis.

Nervous System Disorders: dizziness, conconiton, paresthesia, headache, neuroopathy peripheral, syncope.

Psychiatric Disorders: depression, anxiety, disorientation, suicidal ideation.

Renal and Urinary Disorders: azotemia.

Reproductive System and Breast Disorders: vulvovaginal pruritus.

Respiratory, Thoracic and Mediastinal Disorders: cough, dyspepsia, oropharyngeal pain, asthma, bronchial hyperactivity, epistaxis.

Skin and Subcutaneous Tissue Disorders: rash, hyperhidrosis, pruritus, urticaria.

6.2 Postmarketing Experience

The following adverse reactions have been identified from postmarketing surveillance of rifapentine. Because these reactions are reported from a population of unknown size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome [see Warnings and Precautions (5.3)].

7 DRUG INTERACTIONS

7.1 Protease Inhibitors and Reverse Transcriptase Inhibitors

Rifapentine 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 (5.5) and Clinical Pharmacology (12.3)].

7.2 Fixed-Dose Combination of Elavirenz, Emtricitabine, and Tenofovir

Once-weekly coadministration of 800 mg PRIFTIN with the antiretroviral fixed-dose combination of elavirenz 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 elavirenz, 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. Patients using hormonal contraception should be advised to use an alternative non-hormonal contraceptive method or add a barrier method of contraception during treatment with PRIFTIN [see Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)].

7.4 Cytochrome P450 3A4 and 2C8/9

Rifapentine is an inducer of cytochromes P450 3A4 and P450 2C8/9. Therefore, PRIFTIN may increase the metabolism of other coadministered drugs that are metabolized by these enzymes. Induction of enzyme activities by PRIFTIN occurred within 4 days after the first dose. Enzyme activities returned to baseline levels 14 days after discontinuing PRIFTIN.

Rifapentine has been reported to accelerate the metabolism and may reduce the activity of the following drugs; hence, PRIFTIN may also increase the metabolism and decrease the activity of these drugs. Dosage adjustments of the drugs in Table 4 or of other drugs metabolized by cytochrome P450 3A4 or P450 2C8/9 may be necessary if they are given concurrently with PRIFTIN.

Table 4: Drug Interactions with PRIFTIN: Dosage Adjustment May be Necessary

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples of Drugs Within Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmics</td>
<td>Disopyramide, mexiletine, quinidine</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Chloramphenicol, clarithromycin, dapsone, doxycycline, fluoroquinolones (such as ciprofloxacin)</td>
</tr>
<tr>
<td>Oral Anticoagulants</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>Quinine</td>
</tr>
<tr>
<td>Azole Antifungals</td>
<td>Fluconazole, itraconazole, ketoconazole</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Beta-Blockers</td>
<td>Propranolol</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>Diltiazem, felodipine, verapamil</td>
</tr>
<tr>
<td>Cardiac Glycoside Preparations</td>
<td>Digoxin</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Prednisone</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Clofibrate</td>
</tr>
<tr>
<td>Oral Hypoglycemics</td>
<td>Sulfonylureas (e.g., glyburide, glipizide)</td>
</tr>
<tr>
<td>Hormonal Contraceptives/Progestins</td>
<td>Ethinyl estradiol, levonorgestrel</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>Cyclosporine, tacrolimus</td>
</tr>
<tr>
<td>Methylxanthines</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Narcotic analgesics</td>
<td>Methadone</td>
</tr>
<tr>
<td>Phosphodiesterase-5 (PDE-5) Inhibitors</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>Thyroid preparations</td>
<td>Levothyroxine</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Amitriptyline, nortriptyline</td>
</tr>
</tbody>
</table>

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

Risk Summary

Based on animal data, PRIFTIN may cause fetal harm when administered to a pregnant woman. Available data from clinical trials, case reports, epidemiology studies and postmarketing experience with PRIFTIN use in pregnant women are insufficient to establish a drug-associated risk of major birth defects, adverse maternal or fetal outcomes. In two clinical trials, a total of 59 patients who were treated with rifapentine in combination with other anti-tuberculosis drugs became pregnant. Overall, the reported rate of miscarriage following rifapentine exposure in these two clinical trials did not represent
an increase over the background rate of miscarriage reported in the general population (see Data). There are no associated risks of using active tuberculosis during pregnancy when administered during the last few weeks of pregnancy, PRIFTIN may be associated with maternal postpartum hemorrhage and bleeding in the exposed neonates (see Clinical Considerations). In animal reproduction and developmental toxicity studies, adverse developmental outcomes (including cleft palate or mal-positioned aortic arches) were observed following administration of rifapentine to pregnant rats and rabbits at doses approximately 5.6 and 0.3 to 1.3 times, respectively, of the recommended human dose based on body surface area comparisons (see Data). Based on animal data, advise pregnant women of the risk for fetal harm. As rifapentine is always used in combination with other antituberculosis drugs such as isoniazid, ethambutol, and pyrazinamide, refer to the prescribing information of the other drugs for more information on their associated risks of use during pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In clinical studies, the safety profile in children was similar to that observed in adult patients (see Clinical Pharmacology (12.6)). In pharmacokinetic studies conducted in 2 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 900 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 900 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)).

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 instillation of an activated charcoal slurry into the stomach, may help adsorb any remaining drug from the gastrointestinal tract. Rifapentine and 25-desacetyl rifapentine are 57.7% 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 lactulose, sodium starch glycolate, synthetic red iron oxide, and titanium dioxide.

Rifapentine is a rifamycin derivative and microorganism and has a similar profile of microbiological activity to rifampicin. The molecular weight is 877.04.

The molecular formula is C_{26}H_{34}N_{6}O_{12}.

The chemical name for rifapentine is rifamycin, 3-[([4-cyclopentyl-1-piperazinyl]iminomethyl)- or 3-[N-[4-cyclopentyl-1-piperazinylformimidoyl]rifamycin or 5,6,9,17,19,21-hexahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[N-(4-cyclopentyl-1-piperazinyl)-formimidoyl]-2,7-(epoxypentadeca[1,11,13]trienimino)naphtho[2,1-b]furan-1,11(2H)-dione 21-acetate. It has the following structure:

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rifapentine, a cyclopentyl rifamycin, is an anticytbacterial agent [see Clinical Pharmacology, Microbiology (12.6)].

12.2 Pharmacokinetics

When oral doses of PRIFTIN were administered once daily or once every 72 hours to healthy volunteers for 10 days, single dose AUC_{ss} of rifapentine was similar to its steady-state AUC_{ss} or AUC_{0-72h}

The pharmacokinetic parameters of rifapentine and 25-desacetyl rifapentine on day 10 following oral administration of 600 mg 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_{ss} (µg/mL)</td>
<td>15.05 ± 4.62</td>
<td>6.26 ± 2.06</td>
</tr>
<tr>
<td>AUC (0-72h) µg·h/mL</td>
<td>319.54 ± 91.52</td>
<td>215.88 ± 85.96</td>
</tr>
<tr>
<td>T_{1/2} (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>CIV (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.
Asymptomatic HIV-Infected Volunteers: Following oral administration of a single 600 mg dose of rifapentine, 29% to 36% of asymptomatic HIV-infected volunteers (n=15) under fasting conditions, mean Cmax and AUC0-24 of rifapentine were lower (20%–32%) than that observed in other studies in healthy volunteers (n=55). In a cross-study comparison, mean Cmax and AUC values of the 25-desacetyl rifapentine, when compared to healthy volunteers were higher (6%–21%) in one study (n=20), but lower (15%–16%) in a different study (n=60). The clinical significance of this observation is not known. Food (850 total calories: 33 g protein, 55 g fat, and 58 g carbohydrate) decreases the mean AUC and Cmax of rifapentine observed under fasting conditions in asymptomatic HIV-infected volunteers by about 51% and 53%, respectively.

Drug-Drug Interactions

Isoniazid: Co-administration of PRIFTIN (900 mg single dose) and isoniazid (900 mg single dose), in fasted condition, did not result in any significant change in the exposure of rifapentine and isoniazid compared to when administered alone in fasted condition.

Rifapentine is an inducer of cytochrome P450 3A4 and CYP3A4. Therefore, it may increase the metabolism and decrease the activity of other coadministered drugs that are metabolized by these enzymes. Dosage adjustments of the coadministered drugs may be necessary if they are given concurrently with rifapentine (see Drug Interactions (7.4))

Indinavir: In a study in which 600 mg of rifapentine was administered twice weekly for 14 days followed by PRIFTIN twice weekly plus 800 mg indinavir 3 times a day for an additional 14 days, indinavir Cmax decreased by 55% while AUC reduced by 70%. Clearance of indinavir increased by 3-fold in the presence of PRIFTIN while half-life did not change. But when indinavir was administered for 14 days followed by coadministration with PRIFTIN for an additional 14 days, indinavir did not affect the pharmacokinetics of rifapentine (see Warnings and Precautions (5.5) and Drug Interactions (7.4)).

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 (Table 7). A 15% decrease in efavirenz Cmax and AUC and a 13% decrease in tenofovir Cmax were observed with repeated weekly doses of PRIFTIN (Table 7). No clinically significant change in CD4 cell counts or viral loads were noted.

Mechanism of Action

Rifapentine, a cyclopentyl 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 therapeutic levels, 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-desacetyl metabolite accumulate in human monocyte-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 105 to 106 bacilli. Rifapentine resistance appears to be associated with monotherapy. Therefore, rifapentine should always be used in combination with other antibacterial drugs.

Cross Resistance

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

Suscettibility 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Hepatocellular carcinomas were increased in male NMRI mice (Harlan Winkelmann) which were treated orally with rifapentine for two years at or above doses of 5 mg/kg/day (0.04 times the recommended human dose based on body surface area conversions). In a two year rat study, there was an increase in nasal cavity adenomas in Wistar rats treated orally with rifapentine at 40 mg/kg/day (0.6 times human dose based on body surface area conversions).

Rifapentine was negative in the following genotoxicity tests: in vitro gene mutation assay in bacteria ( Ames test); in vitro point mutation test in Aspergillus nidulans; in vitro gene conversion assay in Saccharomyces cerevisiae host-mediated (mouse) gene conversion assay with Saccharomyces cerevisiae HGPRT 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 (Table 7). A 15% decrease in efavirenz Cmax and AUC and a 13% decrease in tenofovir Cmax were observed with repeated weekly doses of PRIFTIN (Table 7). No clinically significant change in CD4 cell counts or viral loads were noted.

12.4 Microbiology

Mechanism of Action

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Suscettibility 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.
bacteria (Ames test), the in vitro Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyltransferase (CHO/HGPRT) forward mutation assay, and the in vivo mouse bone marrow micronucleus assay. Fertility and reproductive performance were not affected by oral administration of rifapentine to male and female rats at doses of up to 20 mg/kg/day (one-third of the human dose based on body surface area conversions).

14 CLINICAL STUDIES

14.1 Active Pulmonary Tuberculosis

PRIFTIN was studied in two randomized, open-label controlled clinical trials in the treatment of active pulmonary tuberculosis.

The first trial was an open-label, prospective, parallel group, active-controlled trial in HIV-negative patients with active pulmonary tuberculosis. The population mostly comprised Black (approximately 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 groups 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 below contains assessments of sputum conversion at end of treatment (6 months) and relapse rates at the end of follow-up (24 months).

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 HIV-positive patients with active pulmonary tuberculosis. Patients with culture-positive, drug-susceptible pulmonary tuberculosis had who completed the initial 2-month phase of treatment with 4 drugs (rifampin, isoniazid, pyrazinamide, and 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. Enrollment of HIV-infected patients was stopped when 4 of 36 patients in the PRIFTIN combination group relapsed with isolates that were rifampin resistant. 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. Enrollment of HIV-infected patients was stopped when 4 of 36 patients in the PRIFTIN combination group relapsed with isolates that were rifampin resistant.

Table 8 below contains assessments of sputum conversion at the end of treatment (6 months) and relapse rates at the end of follow-up (24 months).

<table>
<thead>
<tr>
<th>Status at End of 6 months of Treatment</th>
<th>PRIFTIN Combination Treatment % and (n/8)</th>
<th>Rifampin Combination Treatment % and (n/8)</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

Table 9: Clinical Outcome in HIV Negative Patients with Active Pulmonary Tuberculosis (Trial 2 (continued))

<table>
<thead>
<tr>
<th>Status Through 24 Month Follow-up²</th>
<th>PRIFTIN Combination Treatment % and (n/8)</th>
<th>Rifampin Combination Treatment % and (n/8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsed</td>
<td>4% (4/234)</td>
<td>5% (2/234)</td>
</tr>
<tr>
<td>Sputum Negative</td>
<td>5% (14/234)</td>
<td>4% (11/234)</td>
</tr>
<tr>
<td>Deaths</td>
<td>3% (7/234)</td>
<td>2% (4/234)</td>
</tr>
</tbody>
</table>

Table 10: Outcomes in Randomized Patients at 33 Months Post Enrollment³

<table>
<thead>
<tr>
<th>Outcome</th>
<th>9INH (n=3074)</th>
<th>Difference, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis n (%)</td>
<td>5 (0.16)</td>
<td>10 (0.32)</td>
</tr>
<tr>
<td>Cumulative TB Rate (%)</td>
<td>0.17</td>
<td>0.35</td>
</tr>
<tr>
<td>Deaths</td>
<td>22 (0.72)</td>
<td>35 (1.14)</td>
</tr>
<tr>
<td>Lost to Follow-Up</td>
<td>220 (10.41)</td>
<td>357 (11.61)</td>
</tr>
</tbody>
</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-resistant. In the 3RPT/INH treatment group, one of the seven cases was rifampin-resistant, isoniazid-susceptible M. bovis infection.

Pediatric substudy

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 373 children in the 3RPT/INH arm and 367 in the 9INH arm. One child in the 9INH group developed tuberculosis (1/367, cumulative rate 0.32%) versus 10 of 3074 patients in the 9INH group (0.32%), for a difference in cumulative rates of 0.17%, 95% CI (0.43, 0.09) (Table 10).

Table 11: Clinical Outcome in HIV Negative Patients with Active Pulmonary Tuberculosis (Trial 2) (continued)

<table>
<thead>
<tr>
<th>Status at End of 4 Months Continuation Phase</th>
<th>PRIFTIN Combination Treatment % and (n/8)</th>
<th>Rifampin Combination Treatment % and (n/8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Response³</td>
<td>93.8% (471/502)</td>
<td>91% (457/502)</td>
</tr>
</tbody>
</table>
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)
   - hives
   - cough with wheezing
   - difficulty breathing
   - red eyes
   - lower blood platelet levels

- **Severe skin reactions.** Serious skin reactions such as Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have happened in some people taking PRIFTIN. Stop taking PRIFTIN right away and call your doctor or get emergency help if you have any of the following symptoms:
   - peeling or bleeding skin
   - sores or blisters on the inside of your mouth
   - swollen face, lips, mouth tongue or throat
   - flu-like symptoms

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 taking PRIFTIN, tell your doctor about all of your medical conditions, including 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. Talk to your healthcare provider about the best way to feed your baby while taking PRIFTIN.

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 Clostridioides 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: allergic reactions and flu-like symptoms; abnormalities such as low red blood cells, low white blood cells, coughing up blood, cough, excessive number of platelets in the blood, increased sweating, high liver function tests, back pain, rash, decreased appetite, joint pain, increased blood urea, and headache.

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.

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

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

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: June 2020

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