DESCRIPTION

RIFAMATE® is a combination capsule containing 300 mg rifampin and 150 mg isoniazid. The capsules also contain the inactive ingredients: colloidal silicon dioxide, FD&C Blue No. 1, FD&C Red No. 40, gelatin, magnesium stearate, sodium starch glycolate, and titanium dioxide.

Rifampin

Rifampin is a semisynthetic antibiotic derivative of rifamycin SV. Rifampin is a red-brown crystalline powder very slightly soluble in water at neutral pH, freely soluble in chloroform, soluble in ethyl acetate and methanol. Its molecular weight is 565 and its chemical formula is C₃₄H₃₅N₇O₁₀₅S. The chemical name for rifampin is either:

\[\text{3-[[4-(methyl-1-piperazinyl)imino]-methyl]-rifamycin} \]

or

\[5,6,9,17,19,21-hexahydroxy-23-methoxy-2,4,12,16,18,20,22-\text{heptamethyl}-8-[\text{4-(4-methyl-1-piperazinyl)}formimido]2,7-(\text{epoxypentadecane})11,13\text{thieniminono]naptho[2,1-b\text{furan-1,11(2H)dione 21-acetate.}}\]

Its structural formula is:

![Chemical Structure of Rifampin](attachment:image.png)

Isoniazid

Isoniazid is the hydrazide of isonicotinic acid. It is a colorless or white crystalline powder or white crystals. It is odorless and slowly affected by exposure to air and light. It is freely soluble in water, sparingly soluble in alcohol and slightly soluble in chloroform and in ether. Its molecular weight is 137.14 and its chemical formula is C₆H₁₂N₂O₂.

The chemical name for isoniazid is 4-pyridinecarboxylic acid, hydrazide and its structural formula is:

![Chemical Structure of Isoniazid](attachment:image.png)

CLINICAL PHARMACOLOGY

General

Rifampin

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

In a study of 14 normal human adult males, peak blood levels of rifampin occurred 1½ to 2 hours following oral administration of two RIFAMATE capsules. The peaks ranged from 6.9 to 14 mcg/mL with an average of 10 mcg/mL.

In healthy adults, the biological half-life of rifampin in serum averages 3.5±0.66 hours after a 600 mg oral dose, with increases up to 5.08±2.45 hours reported after a 900 mg dose. With repeated administration, the half-life decreases and reaches average values of approximately 2 to 3 hours. The half-life does not differ in patients with renal failure at doses not exceeding 600 mg daily, and, consequently, no dosage adjustment is required.

The half-life of rifampin at a dose of 720 mg daily has not been established in patients with renal failure. Following a single 900 mg oral dose of rifampin in patients with varying degrees of renal insufficiency, the mean half-life increased from 3.6 hours in healthy adults to 9.0, 8.4, and 9.4 hours in patients with glomerular filtration rates of 30 to 50 mL/min, less than 30 mL/min, and in anuric patients, respectively. Refer to the WARNINGS section for information regarding patients with hepatic insufficiency.

After absorption, rifampin is rapidly eliminated in the bile, and an enterohepatic circulation ensues. During this process, rifampin undergoes progressive deacetylation so that nearly all the drug in the bile is in this form in about 6 hours. This metabolite has antibacterial activity. Intestinal reabsorption, reduced by deacetylation, is facilitated. Up to 30% of a dose is excreted in the urine, with about half as unchanged drug. Rifampin is widely distributed throughout the body. It is present in effective concentrations in many organs and body fluids, including cerebrospinal fluid. Rifampin is about 80% protein bound. Most of the unbound fraction is not ionized and therefore is diffused freely in tissues.

Pediatrics

In one study, pediatric patients 6 to 58 months old were given rifampin suspended in simple syrup or as dry powder mixed with applesauce at a dose of 10 mg/kg body weight. Peak serum concentrations of 10.7±3.7 and 11.5±5.1 mcg/mL were obtained 1 hour after preprandial ingestion of the drug suspension and the applesauce mixture, respectively. After the administration of either preparation, the t½ of rifampin averaged 2.9 hours. It should be noted that in other studies in pediatric populations, at doses of 10 mg/kg body weight, mean peak serum concentrations of 3.5 mcg/mL to 15 mcg/mL have been reported.

Isoniazid

After oral administration, isoniazid is readily absorbed from the GI tract and produces peak blood levels within 1 to 2 hours which decline to 50% or less within 6 hours. It diffuses readily into all body fluids (cerebrospinal, pleural, and ascitic fluids), tissues, organs, and excreta (saliva, sputum, and feces). Concomitant use with food may reduce the absorption of isoniazid while drug may not be absorbed if isoniazid is not substantially bound to plasma proteins. The drug also passes through the placental barrier and into milk in concentrations comparable to those in the plasma. The plasma half-life of isoniazid in patients with normal renal and hepatic function ranges from 1 to 4 hours, depending on the rate of metabolism. From 50% to 70% of a dose of isoniazid excreted in the urine in 24 hours, mostly as unchanged drug. Isoniazid is metabolized in the liver mainly by acetylation and dehydrazination. The rate of acetylation is genetically determined. Approximately 50% of African Americans and Caucasians are "slow inactivators" and the rest are "rapid inactivators"; the majority of Eskimos and Asians are "rapid inactivators."

The rate of acetylation does not significantly alter the effectiveness of isoniazid. However, slow acetylation may lead to higher blood levels of the drug, and thus an increase in toxic reactions.

Pyridoxine (B₆) deficiency is sometimes observed in adults with high doses of isoniazid and is probably due to its competition with pyridoxal phosphate for the enzyme apotyrophosphatase.

Microbiology

Rifampin and isoniazid at therapeutic levels have demonstrated bactericidal activity against both intracellular and extracellular Mycobacterium tuberculosis organisms. Mechanism of Action

Rifampin

Rifampin inhibits DNA-dependent RNA polymerase activity in susceptible Mycobacterium tuberculosis organisms. Specifically, it interacts with bacterial RNA polymerase, but does not inhibit the mammalian enzyme.

Isoniazid

Isoniazid inhibits the biosynthesis of mycolic acids which are major components of the cell wall of Mycobacterium tuberculosis. Resistance

Organisms resistant to rifampin are likely to be resistant to other rifamycins, β-lactamase production should have no effect on rifampin activity. In the treatment of tuberculosis (see INDICATIONS AND USAGE), the small number of resistant cells present within large populations of susceptible cells can rapidly become predominant. In addition, resistance to rifampin has been determined to occur as single-step mutations of the DNA-dependent RNA polymerase. Since resistance can emerge rapidly, appropriate susceptibility tests should be performed in the event of persistent positive cultures.

Activity in vitro and in vivo

Rifampin has bactericidal activity against slow and intermittently growing Mycobacterium tuberculosis organisms.

Susceptibility Testing

For specific information regarding susceptibility test criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: www.fda.gov/ DRUGS/ INFECTIONDISEASE/ INDICATIONSANDUSAGE/ INDICATIONSANDUSAGE.html

INDICATIONS AND USAGE

In the treatment of tuberculosis, the small number of resistant cells present within large populations of susceptible cells can rapidly become the predominant type. Since resistance can emerge rapidly, susceptibility tests should be performed in the event of persistent positive cultures. Bacteriologic smears or cultures should be obtained before the start of therapy to confirm the susceptibility of the organism to rifampin and isoniazid, and they should be repeated throughout therapy to monitor response to the treatment. If test results show resistance to any of the components
of RIFAMATE and the patient is not responding to therapy, the drug regimen should be modified.

RIFAMATE is indicated for pulmonary tuberculosis in which organisms are susceptible, and when the patient has been titrated on the individual components and it has therefore been established that this fixed dosage combination drug is not recommended for initial therapy of tuberculosis or for preventive therapy.

A three-drug regimen consisting of rifampin, isoniazid, and pyrazinamide (e.g., RIFATER®) is recommended in the initial phase of short-course therapy which is usually continued for 2 months. For the Elimination of Tuberculosis, the American Thoracic Society, and Centers for Disease Control and Prevention recommend that either streptomycin or ethambutol be added as a fourth drug in a regimen containing isoniazid (INH), rifampin, and pyrazinamide for initial treatment of tuberculosis unless the likelihood of INH resistance is low. The presence of these reactivation symptoms of susceptibility testing are known. If community rates of INH resistance are currently less than 4%, an initial treatment regimen with less than four drugs may be considered.

Following the initial phase, treatment should be continued with RIFAMATE for at least 4 months. Treatment should be continued for longer if the patient is still sputum or culture positive, if reactivation is present, or if the patient is HIV positive.

This drug is not indicated for the treatment of meningococcal infections or asymptomatic carriers of Neisseria meningitidis to eliminate meningococci from the nasopharynx.

CONTRAINDICATIONS

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

Rifampin

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

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

Rifampin is contraindicated in patients receiving praziquantel since therapeutically effective blood levels of praziquantel may not be achieved. In patients receiving rifampin who need immediate treatment with praziquantel alternative agents should be considered. However, if treatment with praziquantel is necessary, rifampin should be discontinued 4 weeks before administration of praziquantel. Treatment with rifampin can then be restarted one day after completion of praziquantel treatment.

Isoniazid

Other contraindications include patients with severe hepatic damage; severe adverse reactions to isoniazid, such as drug fever, chills, and arthritis; patients with acute liver disease of any etiology; and patients with acute gout.

WARNING

RIFAMATE (rifampin and isoniazid capsules USP) is a combination of two drugs, each of which has been associated with liver dysfunction.

Systemic hypersensitivity reactions were reported with both components of RIFAMATE (rifampin and isoniazid). Signs and symptoms of hypersensitivity reactions may include fever, rash, urticaria, angioedema, hypotension, acute bronchospasm, conjunctivitis, thrombocytopenia, neutropenia, elevated liver transaminases or flu-like syndrome (weakness, fatigue, muscle pain, nausea, vomiting, headache, chills, aches, itching, sweats, dizziness, shortness of breath, chest pain, cough, syncope, palpitations). Manifestations of hypersensitivity reactions, such as fever, urticaria, angioedema or laboratory abnormalities (including eosinophilia, liver abnormalities) may be present even though rash is not evident. Monitor patients receiving RIFAMATE for signs and/or symptoms of hypersensitivity reactions. If these signs or symptoms occur, discontinue RIFAMATE and administer supportive measures.

Cases of severe cutaneous adverse reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been reported with both components of RIFAMATE (rifampin and isoniazid). If symptoms or signs of severe cutaneous adverse reactions develops, discontinue RIFAMATE immediately and institute appropriate therapy.

Rifampin

Rifampin has been shown to produce liver dysfunction. There have been fatalities associated with jaundice in patients with liver disease or receiving rifampin concomitantly with other hepatotoxic agents. Because RIFAMATE contains both rifampin and isoniazid, it should only be given with caution and under strict medical supervision to patients with impaired liver function. In these patients, careful monitoring of liver function, especially serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) should be carried out prior to therapy and then every 2 to 4 weeks during therapy. If signs of hepatic cellular damage occur, RIFAMATE should be withdrawn.

In some cases, hyperbilirubinemia resulting from competition between rifampin and bilirubin for excretory pathways of the liver at the cell level can occur in the early days of treatment. An isolated report showing a moderate rise in bilirubin and/or transaminase level is not itself an indication for interrupting treatment; rather, the decision should be made after repeating the tests, noting trends in the levels, and considering them in conjunction with the patient’s clinical condition.

Rifampin has enzyme-inducing properties, including induction of delta alpha levulinic acid synthetase. Isolated reports have associated porphyria exacerbation with rifampin administration.

Cases of severe cutaneous adverse reactions (SCAR) such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome have been reported with rifampin. If symptoms or signs of severe cutaneous adverse reactions develops, discontinue RIFAMATE immediately and institute appropriate therapy.

Rifampin may cause vitamin K–dependent coagulation disorders and bleeding (see ADVERSE REACTIONS). Monitor coagulation tests during rifampin treatment (prothrombin time and other coagulation tests) in patients at risk of vitamin K deficiency (such as those with chronic liver disease, poor nutritional status, on prolonged antibacterial drugs or anticoagulants). Consider discontinuation of RIFADIN if abnormal coagulation tests or bleeding occur. Supplemental vitamin K administration should be considered when appropriate.

Postmarketing reports suggest that concomitant administration of high doses of cefazolin and rifampin may prolong the prothrombin time, leading to severe vitamin K–dependent coagulopathy of patients who may be lifetime-timed or fatal. Avoid concomitant use of cefazolin and rifampin in patients at increased risk for bleeding. If no alternative treatment options are available, closely monitor prothrombin time and other coagulation tests, and administer vitamin K as indicated.

Isoniazid

(See the boxed WARNING.)

Since RIFAMATE contains isoniazid, ophthalmologic examinations (including ophthalmoscopy) should be done before treatment is started and periodically thereafter, even without ocular symptoms. Severe cutaneous reactions including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Nekrolysis (TEN), some with a fatal outcome, have been reported with the use of isoniazid (see ADVERSE REACTIONS). Monitor for skin reactions and advise patients to discontinue therapy if skin rash, desquamation or mucosal lesions immediately. Discontinue RIFAMATE if these reactions occur.

PRECAUTIONS

General

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

Rifampin

For the treatment of tuberculosis, rifampin is usually administered on a daily basis. Doses of rifampin greater than 600 mg given once or twice weekly have resulted in a higher incidence of the flu-like syndrome (fever, malaise, and influenza-like symptoms) (fever, chills, and malaise), hematopoietic reactions (leukopenia, thrombocytopenia, or acute hemolytic anemia), cutaneous, gastrointestinal, and hepatic reactions, shortness of breath, shock, anaphylaxis, and other hypersensitivity reactions. Rare cases of renal failure that required dialysis of rifampin 600 mg plus isoniazid 15 mg/kg are much better tolerated.

Rifampin is not recommended for intermittent therapy; the patient should be cautioned against intentional or accidental interruption of the daily dosage regimen since rare renal hypersensitivity reactions have been reported when therapy was resumed in such cases.

Rifampin has enzyme induction properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones, and vitamin D.

Isoniazid

All drugs should be stopped and an evaluation of the patient should be made at the first sign of a hypersensitivity reaction.

Use of RIFAMATE, because it contains isoniazid, should be carefully monitored in the following:

1. Patients who are receiving phenytoin (diphenylhydantoin) concurrently. Isoniazid may decrease the excretion of phenytoin or may enhance its effects. To avoid phenytoin intoxication, appropriate adjustment of the anticonvulsant dose should be made.

2. Daily users of alcohol. Daily ingestion of alcohol may be associated with a higher incidence of isoniazid hepatitis.

3. Patients with current chronic liver disease or severe renal dysfunction.

Information for Patients

Food Interactions

Because isoniazid has some monoamine oxidase inhibiting activity, an interaction with tyramine-containing foods (cheese, red wine) may occur. Diamine oxidase may also be inhibited, causing an exaggerated response to foods. Diamine oxidase is also inhibited by foods containing histamine (e.g., skipjack, tuna, other tropical fish). Tyramine and histamine-containing foods should be avoided in patients receiving RIFAMATE.

RIFAMATE, because it contains rifampin, may produce a discoloration (yellow, orange, red, brown) of the teeth, urine, sweat, sputum, and tears, and the patient should be forewarned of this. Soft contact lenses may be permanently stained.

Rifampin is a well characterized and potent inducer of drug metabolizing enzymes and transporters and might therefore decrease concomitant drug exposure and efficacy (see DRUG INTERACTIONS). Therefore patients should be advised not to take any other medication without medical advice.

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

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

Instruct patients to notify their physician immediately if they experience any of the following: rash with fever or blisters, with or without peeling skin, fever or swollen lymph nodes, loss of appetite, malaise, nausea and vomiting, darkened urine, yellowish discoloration of the skin and eyes, cough, shortness of breath, wheezing, pain or swelling of the joints.

Compliance with the full course of therapy must be emphasized, and the importance of not missing any doses must be stressed.

Laboratory Tests

Adults treated for tuberculosis with RIFAMATE should have baseline measurements of hepatic enzymes, bilirubin, serum creatinine, a complete blood count (CBC) and platelet count (or estimate), and blood uric acid. Patients should be seen at least monthly during therapy and should be specifically questioned concerning symptoms associated with adverse reactions. All patients with baseline abnormalities should have follow-up, including laboratory testing, if necessary. Routine laboratory monitoring for toxicity in people with normal baseline measurements is generally not necessary.

Drug Interactions

Rifampin

Pharmacodynamic Interactions

Healthy subjects who received rifampin 600 mg once daily concomitantly with saquinavir 1000 mg/ritonavir 100 mg twice daily (ritonavir-boosted saquinavir) developed severe
monitoring, unless otherwise specified. When rifampin is given concomitantly with other hepatotoxic medications such as halothane or isoniazid, the potential for hepatotoxicity is increased. Avoid concomitant use of RIFAMATE with halothane. Monitor patients receiving RIFAMATE for hepatotoxicity. (See the boxed WARNING.)

Induction of drug metabolizing enzymes and transporter systems

Drug metabolizing enzymes and transporters affected by rifampin include cytochromes P450 (CYP) 1A2, 2B6, 2C9, 2C19, and 3A4, UDP-glucuronosyltransferases (UGT), sulfotransferases, carboxylesterases, and transporters including P-glycoprotein (P-gp) and multidrug resistance-associated protein 2 (MRP2). Most drugs are substrates for one or more of these enzyme or transporter pathways, and these pathways may be induced by rifampin simultaneously. Therefore, rifampin may accelerate the metabolism and reduce the activity of certain concomitantly used drugs, and has the potential to perpetuate clinically important drug-drug interactions against many drugs and across many drug classes (Table 1).

Table 1 summarizes the effect of rifampin on other drugs or drug classes. Adjust dosages of concomitant drugs based on approved drug labeling and if applicable, therapeutic drug monitoring, unless otherwise specified.

Table 1: Drug Interactions with Rifampin that Affect Concomitant Drug Concentrations

<table>
<thead>
<tr>
<th>Drug or Drug Class and Prevention or Management</th>
<th>Clinical Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiretrovirals</strong></td>
<td></td>
</tr>
<tr>
<td>Treatment or Management</td>
<td></td>
</tr>
<tr>
<td>Predonavir</td>
<td>Decrease AUC by 72%</td>
</tr>
<tr>
<td>Darunavir</td>
<td>Substantial decrease in exposure, which may result in loss of therapeutic effect and development of resistance.</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>Decrease AUC by 82%</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Decrease AUC by 70%</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Coadministration may result in severe hepatocellular toxicity.</td>
</tr>
<tr>
<td><strong>Antiretrovirals</strong></td>
<td></td>
</tr>
<tr>
<td>Prevention or Management: Avoid concomitant use</td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Decrease AUC by 47%</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Decrease AUC by 92%</td>
</tr>
<tr>
<td>Elaviranz</td>
<td>Decrease AUC by 26%</td>
</tr>
<tr>
<td><strong>Hepatitis C Antiviral</strong></td>
<td></td>
</tr>
<tr>
<td>Prevention or Management: Avoid concomitant use</td>
<td></td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Decrease AUC by 79%</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Decrease AUC by 48%</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Decrease AUC by 72%</td>
</tr>
<tr>
<td>Coadministration of sofosbuvir with rifampin, may decrease sofosbuvir plasma concentrations, leading to reduced therapeutic effect of sofosbuvir.</td>
<td></td>
</tr>
<tr>
<td>Telaprevir</td>
<td>Decrease AUC by 92%</td>
</tr>
<tr>
<td><strong>Systemic Hormonal Contraceptives</strong></td>
<td></td>
</tr>
<tr>
<td>Prevention or Management: Advise patients to change to non-hormonal methods of birth control during rifampin therapy</td>
<td></td>
</tr>
<tr>
<td>Estrogens</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Progestins</td>
<td></td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
</tr>
<tr>
<td>Phenytion</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td><strong>Antiarrhythmics</strong></td>
<td></td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Mexilidene</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Decrease AUC by 50%–67%</td>
</tr>
<tr>
<td>Ticainide</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td><strong>Antiestrogens</strong></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Decrease AUC by 86%</td>
</tr>
<tr>
<td>Toremifene</td>
<td>Decrease steady state concentrations of toremifene in serum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug or Drug Class and Prevention or Management</th>
<th>Clinical Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Decrease plasma concentrations by 70%</td>
</tr>
<tr>
<td><strong>Antifungals</strong></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Decrease AUC by 23%</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
</tr>
<tr>
<td>Itraconazole Prevention or Management: Not recommended 2 weeks before and during iraconazole treatment</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td><strong>Beta-blockers</strong></td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td><strong>Benzodiazepine-related drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Zopiclone</td>
<td>Decrease AUC by 82%</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Decrease AUC by 73%</td>
</tr>
<tr>
<td><strong>Calcium Channel Blockers</strong></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
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<tr>
<td>Prednisolone</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td><strong>Cardiac Glycosides</strong></td>
<td></td>
</tr>
<tr>
<td>Digoxin Prevention or Management: Measure serum digoxin concentrations before initiating rifampin. Continue monitoring and increase digoxin dose by approximately 20%–40% as necessary.</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td><strong>Fluoroquinolones</strong></td>
<td></td>
</tr>
<tr>
<td>Pefloxacin</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Mofoxacin</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td><strong>Oral Hypoglycemic Agents (e.g. sulfonylureas)</strong></td>
<td></td>
</tr>
<tr>
<td>Glyburide</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Glipizide</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td><strong>Immunosuppressive Agents</strong></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td><strong>Tacrolimus</strong></td>
<td></td>
</tr>
<tr>
<td>Prevention or Management: Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when rifampin and tacrolimus are used concomitantly.</td>
<td>Decrease AUC by 56%</td>
</tr>
<tr>
<td><strong>Narcotic Analgesics</strong></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Decrease AUC by 86%</td>
</tr>
<tr>
<td>Morphine</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td><strong>Selective 5-HT3 Receptor Antagonists</strong></td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Decrease exposure</td>
</tr>
</tbody>
</table>
Table 1: Drug Interactions with Rifampin that Affect Concomitant Drug Concentrations (continued)

<table>
<thead>
<tr>
<th>Drug or Drug Class and Prevention or Management</th>
<th>Clinical Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins Metabolized by CYP3A4</td>
<td></td>
</tr>
<tr>
<td>Cholesterol lowering drugs</td>
<td>Increase exposure</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Increase exposure</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Decrease elimination half-life of isoniazid</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>lovastatin</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Mevinclon</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Tricarboxylic Antidepressants</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Nortriptylinea</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Other Drugs</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Decrease active metabolite exposure</td>
</tr>
<tr>
<td>Chlororamphenicol</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Doxycyclineb</td>
<td>Decrease exposure</td>
</tr>
<tr>
<td>Irinotecanb Prevention or Management: Avoid the use of rifampin, strong CYP3A4 inducer, if possible. Substituting non-enzyme inducing therapies at least 2 weeks prior to initiation of irinotecan therapy</td>
<td>Decrease irinotecan and active metabolite exposure</td>
</tr>
<tr>
<td>Quinine Prevention or Management: Avoid concomitant use</td>
<td>Decrease AUC by 75%–85%</td>
</tr>
</tbody>
</table>
|Theophylline                                   | Decrease exposure by 20% to 40%

Levotheroxine Decrease exposure

Losartan Parent Decrease AUC by 30%

Active metabolite (E3174) Decrease AUC by 40%

Methadone In patients well-stabilized on methadone, concomitant administration of rifampin resulted in a marked reduction in serum methadone levels and a concurrent appearance of withdrawal symptoms.

Praziquantel Prevention or Management: Concomitant use is contraindicated (See CONTRAINDICATIONS) Decrease plasma praziquantel concentrations to undetectable levels.

Quinine Prevention or Management: Avoid concomitant use Decrease AUC by 75%–85%

Telithromycin Decrease AUC by 86%

Theophylline Decrease exposure by 20% to 40%

AUC = area under the time-concentration curve

*Administered with rifampin 600 mg daily, unless otherwise specified
†Rifampin dosage used concomitantly with the drug(s) is not specified in the proposed package insert.
‡Administered with rifampin 300 mg daily
§Administered with rifampin 450 mg daily
¶Administered with rifampin 1200 mg daily
\Rifampin 1200 mg administered as a single oral dose of nifedipine 10 mg
\Numerous cases in the literature describe a decrease in glucocorticoid effect when used concomitantly with rifampin. The literature contains reports of acute adrenal crisis or adrenal insufficiency induced by the combination of rifampin-isoniazid-ethambutol or rifampin-isoniazid in patients with Addison’s disease.
\Administered with rifampin 900 mg daily
\A tuberculosis treatment regimen including rifampin (600 mg/day) isoniazid (300 mg/day), pyrazinamide (500 mg 3x per day), and pyridoxine (25 mg) was associated with higher than expected doses of nortriptyline were required to obtain a therapeutic drug level. Following the discontinuation of rifampin, the patient became drowsy and the serum nortriptyline levels rose precipitously (3-fold) into the toxic range.
\Concomitant use with rifampin in 2 children
\Administered with an antibiotic regimen including rifampin (450 mg/day), isoniazid (300 mg/day), and streptomycin (0.5 g/day) IM

Effect of Other Drugs on Rifampin
Concomitant use with antacids may reduce the absorption of rifampin which may reduce the efficacy of RIFAMATE. Administer RIFAMATE at least 1 hour before the ingestion of antacids.

Concomitant use with probenicid and cotrimoxazole increase the concentration of rifampin which may increase the risk of RIFAMATE toxicities. Monitor for adverse reactions associated with in RIFAMATE during coadministration.

Other Interactions
Atovaquone
Concomitant use of rifampin with atovaquone decrease concentrations of atovaquone and increase concentrations of rifampin which may increase the risk of RIFAMATE toxicities. Coadministration of rifampin with atovaquone is not recommended.

Isoniazid
Pharmacodynamic Interactions
Concomitant use with daily ingestion of alcohol may be associated with a higher incidence of isoniazid hepatitis. Concomitant use of isoniazid with rifampin may increase the hepatotoxicity of both drugs. Monitor Patients receiving both rifampin and isoniazid as in RIFAMATE for hepatotoxicity.

Concomitant use may exaggerate the CNS effects of meperidine (drowsiness), cyclizine (dizziness, drowsiness), and disulfiram (acute behavioral and coordination changes).

Concomitant use with levodopa may produce symptoms of excess catecholamine stimulation (agitation, flushing, palpitations) or lack of levodopa effect.

Concomitant use with oral hypoglycemics may produce hyperglycemia and lead to loss of glucose control.

Concomitant use with enflurane may produce high concentrations of hydrazine that facilitate defluorination of enflurane due to fast acetylation of isoniazid. Monitor renal function.

Pharmacokinetic Interactions
Effect of Isoniazid on Other Drugs
Inhibition of drug metabolizing enzymes
Isoniazid is known to inhibit certain cytochrome P-450 enzymes (e.g., CYP1A2, CYP2C9, CYP2C19, CYP3A4). Concomitant use may decrease elimination of drugs metabolized by these enzymes which may increase the risk of toxicities of these drugs. Adjust dosages of rifampin by these enzymes based on approved drug labeling and if applicable, therapeutic drug monitoring.

Isoniazid has been reported to inhibit the metabolism of the following drugs: anticonvulsants (e.g., carbamazepine, phenytoin, primidone, valproic acid, benzodiazepines [e.g., diazepam], haloperidol, ketocazole, theophylline, and warfarin). Therefore, isoniazid may increase the risk of toxicities of these drugs. Adjust dosages of drugs metabolized by these enzymes based on approved drug labeling and if applicable, therapeutic drug monitoring.

Concomitant use with RIFAMATE, which also contains rifampin (detector), on the metabolism of these drugs is unknown.

Other Interactions
Antacid
Concomitant use with antacid may reduce the absorption of isoniazid which may reduce RIFAMATE efficacy. Administer RIFAMATE at least 1 hour before use of antacids.

Corticosteroids
Concomitant use with corticosteroids (e.g., prednisolone) may decrease the serum concentration of isoniazid by increasing acetylation rate and/or renal clearance which may reduce RIFAMATE efficacy.

Para-aminosalicylic acid
Concomitant use with para-aminosalicylic acid may increase the plasma concentration and elimination half-life of isoniazid by competition of acetylating enzymes which may increase the risk of RIFAMATE toxicities.

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

Therapeutic levels of rifampin have been shown to inhibit standard microbiological assays for serum folate and vitamin B12. Therefore, alternative assay methods should be considered. Transient abnormalities in liver function tests (e.g., elevation in serum bilirubin, alkaline phosphatase and serum transaminases), and reduced biliary excretion of contrast media used for visualization of the gallbladder have also been observed. Therefore, these tests should be performed before the morning dose of RIFAMATE.

Rifampin and isoniazid have been reported to alter vitamin D metabolism. In some cases, reduced levels of circulating 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D have been accompanied by reduced serum calcium and phosphate, and elevated parathyroid hormone.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Increased frequency of chromosomal aberrations was observed in vitro in lymphocytes obtained from patients treated with combinations of rifampin, isoniazid, and pyrazinamide (or combinations of streptomycin, rifampin, isoniazid, and pyrazinamide).

Rifampin
A few cases of accelerated growth of lung carcinoma have been reported in man, but a causal relationship with the drug has not been established. Hepatomas were increased in female (C3Hf/DP) mice dosed for 60 weeks with rifampin followed by an observation period of 46 weeks, at 20 to 120 mg/kg (equivalent to 0.1 to 0.5 times the maximum dosage used clinically, based on body surface area comparisons). There was no evidence of tumorigenicity in male C3HfIDF mice or in similar studies in BALB/c mice, or in two year studies in Wistar rats.

There was no evidence of mutagenicity in both prokaryotic (Salmonella typhi, Eschenichia coli) and eukaryotic (Saccharomyces cerevisiae) bacteria, Drosophila melanogaster, or ICR/Ha Swiss mice. An increase in chromatid breaks was noted when whole blood cell cultures were treated with rifampin.

Isoniazid
Isoniazid has been reported to induce pulmonary tumors in a number of strains of mice. 

Pregnancy
Teratogenic Effects
Although animal reproduction studies have not been conducted with RIFAMATE, teratogenic effects (including cleft palate and spina bifida) have been observed in rodents treated with rifampin at doses 0.2 to 2 times the maximum recommended human dose, based on body surface area comparisons. There are no adequate and well-controlled
studies of Rifamate in pregnant women. Rifamate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Rifampin

Congenital malformations, primarily spina bifida, were increased in the offspring of pregnant rats given rifampin during organogenesis at oral doses of 150 to 250 mg/kg/day (about 1 to 2 times the maximum recommended human dose based on body surface area comparisons). Cleff palate was increased in a dose-dependent fashion in fetuses of pregnant mice treated at oral doses of 50 to 200 mg/kg (about 0.2 to 0.8 times the maximum recommended human dose based on body surface area comparisons). Infant monkeys given orally to pregnant rabbits given rifampin at oral doses up to 200 mg/kg/day (about 3 times the maximum recommended daily human dose based on body surface area comparisons). Although there are no adequate and well-controlled studies in pregnant women, rifampin has been reported to cross the placental barrier and appear in cord blood.

Isoniazid

It has been reported that in both rats and rabbits, isoniazid may exert an embriocidal effect when administered orally during pregnancy, although no isoniazid-related congenital anomalies have been found in reproduction studies in mammalian species (mice, rats, and rabbits).

Pregnancy

Non-Teratogenic Effects

When administered during the last few weeks of pregnancy, rifampin can cause postnatal hemorrhages in the mother and infant for which treatment with vitamin K may be indicated.

Rifampin

When administered during the last few weeks of pregnancy, rifampin can cause postnatal hemorrhages in the mother and infant. In this case, treatment with vitamin K may be indicated for postnatal hemorrhage.

Nursing Mothers

Because of the potential for tumorigenicity shown for rifampin in animal studies, and since rifampin and isoniazid are known to cross the placental barrier and to pass into maternal breast milk, a decision should be made whether to discontinue nursing or to discontinue Rifamate, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients under the age of 15 have not been established. (See CLINICAL PHARMACOLOGY, General; See also DOSAGE AND ADMINISTRATION.)

Geriatric Use

Clinical studies of Rifamate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Caution should therefore be observed in using rifampin and isoniazid in elderly patients. (See WARNINGS.)

ADVERSE REACTIONS

Rifampin

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

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

Hematologic: thrombocytopenia has occurred primarily with high dose intermittent therapy, but has also been noted after resumption of interrupted treatment. It rarely occurs during weekly dosage regimens. This effect is reversible if the drug is discontinued as soon as purpura occurs. Cerebral hemorrhage and fatalities have been reported when rifampin administration has been continued or resumed after the appearance of purpura. Rare reports of disseminated intravascular coagulation have been observed.

Neuromuscular: episodes of fever, chills, headache, dizziness, and bone pain), shortness of breath, acidosis, and gynecomastia.

Miscellaneous: rash. More serious cutaneous reactions which may be due to hypersensitivity occur but these are uncommon. The incidence is higher in alcoholics and diabetics, and is usually preceded by paresthesia of the feet and hands. The incidence is higher in “slow inactivators.”

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

Gastrointestinal: pancreatitis, nausea, vomiting, and epigastric distress.

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

Hematologic: agranulocytosis, hemolytic sideroblastic or aplastic anemia, thrombocytopenia, and eosinophilia.

Hypersensitivity reactions: fever, skin eruptions (morbilliform, maculopapular, purpuric, or exfoliative), lymphadenopathy, anaphylactic reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis (see WARNINGS, Isoniazid), Drug Reaction with Eosinophilia and Systemic Symptoms syndrome (see WARNINGS), and vasculitis.

Metabolic and endocrine: pyridoxine deficiency, pellagra, hyperglycemia, metabolic acidosis, and gynecomastia.

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Acute Toxicity

Rifampin

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

Isoniazid

Isoniazid overdose produces signs and symptoms within 30 minutes to 3 hours. Nausea, vomiting, dizziness, slurring of speech, blurring of vision, visual hallucinations (including bright colors and strange designs), are among the early manifestations. With marked overdose, respiratory distress and CNS depression, progressing rapidly from stupor to profound coma, are to be expected, along with severe, intractable seizures. Severe metabolic acidosis, acetonuria, and hyperglycemia are typical laboratory findings.

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Isoniazid

Untreated or inadequately treated cases of gross isoniazid overdosage can be fatal, but good response has been reported in most patients treated within the first few hours after doses ingestion. Ingested acetylated, as little as 1.5 g isoniazid may cause toxicity in adults. Doses of 35 to 40 mg/kg have resulted in seizures. Ingestion of 80 to 150 mg/kg isoniazid has been associated with severe toxicity and, if untreated, significant mortality.

Treatment

The patient should be secured and adequate respiratory exchange established. Only if the patient appears to be gasping (avagination) be attempted; it may be difficult because of seizures. Since nausea and vomiting are likely to be present, gastric lavage is probably preferable to induction of emesis.

Gastric lavage should be performed for immediate determination of gases, electrolytes, BUN, glucose, etc. Blood should be typed and cross-matched in preparation for possible hemodialysis.

Gastric lavage within the first 2 to 3 hours after ingestion should not be attempted unless convulsions are under control. To treat convulsions, administer IV diazepam or short-acting barbiturates, and IV pyridoxine (usually 1 mg/1 mg isoniazid ingested). Activated charcoal slurry instilled into the stomach following evacuation of gastric contents can help absorb any remaining drug in the GI tract. Antiemetic medication may be required to control severe nausea and vomiting.
RAPID CONTROL OF METABOLIC ACIDOSIS IS FUNDAMENTAL TO MANAGEMENT.
Intravenous sodium bicarbonate should be given at once and repeated as needed, adjusting subsequent dosage on the basis of laboratory findings (i.e., serum sodium, pH, etc.).
Forced osmotic diuresis must be started early and should be continued for some hours after clinical improvement to hasten renal clearance of drug and help prevent relapse. Fluid intake and output should be monitored.
Bile drainage may be indicated in presence of serious impairment of hepatic function lasting more than 24–48 hours. Under these circumstances and for severe cases, extracorporeal hemodialysis may be required; if this is not available, peritoneal dialysis can be used along with forced diuresis.
Along with measures based on initial and repeated determination of blood gases and other laboratory tests as needed, meticulous respiratory and other intensive care should be utilized to protect against hypoxia, hypotension, aspiration, pneumonitis, etc.
Untreated or inadequately treated cases of gross isoniazid overdosage can terminate fatally, but good response has been reported in most patients brought under adequate treatment within the first few hours after drug ingestion.
DOSAGE AND ADMINISTRATION
A three-drug regimen consisting of rifampin, isoniazid, and pyrazinamide (e.g., Rifater®) is recommended in the initial phase of short-course therapy which is usually continued for 2 months. The Advisory Council for the Elimination of Tuberculosis, the American Thoracic Society, and Centers for Disease Control and Prevention recommend that either streptomycin or ethambutol be added as a fourth drug in a regimen containing isoniazid (INH), rifampin, and pyrazinamide for initial treatment of tuberculosis unless the likelihood of INH or rifampin resistance is very low. The need for a fourth drug should be reassessed when the results of susceptibility testing are known. If community rates of INH resistance are currently less than 4%, an initial treatment regimen with less than four drugs may be considered. Following the initial phase, treatment should be continued with Rifamate for at least 4 months. Treatment should be continued for longer if the patient is still sputum or culture positive, if resistant organisms are present, or if the patient is HIV positive. Concomitant administration of pyridoxine (B<sub>6</sub>) is recommended in the marauished, in those predisposed to neuropathy (e.g., alcoholics and diabetics), and in adolescents. See CLINICAL PHARMACOLOGY, General, for dosing information in patients with renal failure.
Adults
Two Rifamate (rifampin and isoniazid capsules USP) capsules (600 mg rifampin, 300 mg isoniazid) once daily, administered one hour before or two hours after a meal.
Pediatric Patients
The ratio of the drugs in Rifamate may not be appropriate in pediatric patients under the age of 15 (e.g., higher mg/kg doses of isoniazid are usually given in pediatric patients than adults).
HOW SUPPLIED
Capsules (opaque red), imprinted “RIFAMATE” on both ends of the capsule, containing 300 mg rifampin and 150 mg isoniazid; bottles of 60 (NDC 0068-0509-60).
Storage
Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from excessive humidity.
Manufactured for:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
A SANOFI COMPANY

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