RIFATER®
(rifampin, isoniazid and pyrazinamide USP)
Tablets

WARNING
Severe and sometimes fatal hepatitis associated with isoniazid therapy may occur and may develop even after many months of treatment. The risk of developing hepatitis is age related. Approximate case rates by age are: 0 per 1,000 for persons under 20 years of age, 3 per 1,000 for persons in the 20 to 34 year age group, 12 per 1,000 for persons in the 35 to 49 year age group, 23 per 1,000 for persons in the 50 to 64 year age group, and 8 per 1,000 for persons over 65 years of age. The risk of hepatitis is increased with daily consumption of alcohol. Precise data to provide a fatality rate for isoniazid-related hepatitis is not available; however, in a U.S. Public Health Service Surveillance Study of 13,838 persons taking isoniazid, there were 8 deaths among 174 cases of hepatitis.

Therefore, patients given isoniazid should be carefully monitored and interviewed at monthly intervals. Serum transaminase concentration becomes elevated in about 10% to 20% of patients, usually during the first few months of therapy, but it can occur at any time. Usually enzyme levels return to normal despite continuance of drug, but in some cases progressive liver dysfunction occurs. Patients should be instructed to report immediately any of the prodromal symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea, or vomiting. If these symptoms appear or if signs suggestive of hepatic damage are detected, isoniazid should be discontinued promptly since continued use of the drug in these cases has been reported to cause a more severe form of liver damage.

Patients with tuberculosis should be given appropriate treatment with alternative drugs. If isoniazid must be reinstituted, it should be reinstituted only after symptoms and laboratory abnormalities have cleared. The drug should be restarted in very small and gradually increasing doses and should be withdrawn immediately if there is any indication of recurrent liver involvement. Treatment should be deferred in persons with acute hepatic diseases.

DESCRIPTION
RIFATER (rifampin/isoniazid/pyrazinamide USP) tablets are combination tablets containing 120 mg rifampin, 50 mg isoniazid, and 300 mg pyrazinamide for use in antibacterial therapy. The tablets also contain as inactive ingredients: povidone, carboxymethyl cellulose sodium, calcium stearate, sodium lauryl sulfate, sucrose, talc, acacia, titanium dioxide, kaolin, magnesium carbonate, colloidal silicon dioxide, dried aluminum hydroxide gel, ferric oxide, black iron oxide, carnauba wax, white beeswax, colophony, hard paraffin, lecithin, shellac, and propylene glycol. The RIFATER triple therapy combination was developed for dosing convenience.

Rifampin

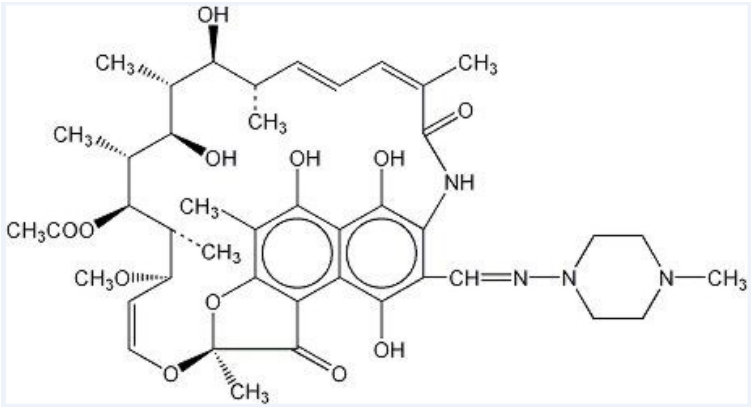
Rifampin is a semisynthetic antibiotic derivative of rifamycin SV. Rifampin is a red-brown crystalline powder very slightly soluble in water at neutral pH, freely soluble in chloroform, soluble in ethyl acetate and methanol. Its molecular weight is 822.95 and its chemical formula is $C_{43}H_{58}N_4O_{12}$. The chemical name for rifampin is either:

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–heptamethyl-8-[N-(4-methyl-1-piperazinyl) formimidoyl]-2,7-(epoxypentadeca [1,11,13]trienimino)naphtho[2,1-*b*]furan-1,11(2H)-dione 21-acetate.

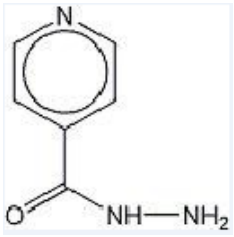
Its structural formula is:



Isoniazid

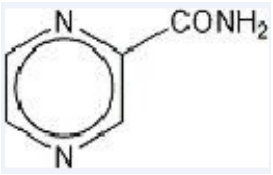
Isoniazid is the hydrazide of isonicotinic acid. It is a colorless or white crystalline powder or white crystals. It is odorless and slowly affected by exposure to air and light. It is freely soluble in water, sparingly soluble in alcohol and slightly soluble in chloroform and in ether. Its molecular weight is 137.14 and its chemical formula is $C_6H_7N_3O$.

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



Pyrazinamide

Pyrazinamide, the pyrazine analogue of nicotinamide, is a white, crystalline powder, stable at room temperature, and sparingly soluble in water. The chemical name for pyrazinamide is pyrazinecarboxamide and its molecular weight is 123.11. Its chemical formula is $C_5H_5N_3O$ and its structural formula is:



CLINICAL PHARMACOLOGY

General

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

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

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

Rifampin

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

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

filtration rates of 30-50 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 is reduced by deacetylation, and elimination is facilitated. Up to 30% of a dose is excreted in the urine, with about half as unchanged drug.

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 $t_{1/2}$ of rifampin averaged 2.9 hours. It should be noted that in other studies in pediatric populations, at doses of 10 mg/kg body weight, mean peak serum concentrations of 3.5 mcg/mL to 15 mcg/mL have been reported.

Isoniazid
After oral administration, isoniazid is readily absorbed from the GI tract and produces peak blood levels within 1 to 2 hours which decline to 50% or less within 6 hours. It diffuses readily into all body fluids (cerebrospinal, pleural, and ascitic fluids), tissues, organs, and excreta (saliva, sputum, and feces). Concomitant use with food may reduce the absorption of isoniazid which may reduce RIFATER efficacy.

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 is excreted in the urine within 24 hours, mostly as metabolites.

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 (B_6) deficiency is sometimes observed in adults with high doses of isoniazid and is probably due to its competition with pyridoxal phosphate for the enzyme apotryptophanase.

Pyrazinamide

Pyrazinamide is well absorbed from the gastrointestinal tract and attains peak plasma concentrations within 2 hours. Plasma concentrations generally range from 30 to 50 mcg/mL with doses of 20 to 25 mg/kg. It is widely distributed in body tissues and fluids including the liver, lungs, and cerebrospinal fluid (CSF). The CSF concentration is approximately equal to concurrent steady-state plasma concentrations in patients with inflamed meninges. Pyrazinamide is approximately 10% bound to plasma proteins. The plasma half-life of pyrazinamide is 9 to 10 hours in patients with normal renal and hepatic function. The half-life of the drug may be prolonged in patients with impaired renal or hepatic function. Pyrazinamide is hydrolyzed in the liver to its major active metabolite, pyrazinoic acid. Pyrazinoic acid is hydroxylated to the main excretory product, 5-hydroxypyrazinoic acid.

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

Microbiology

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*.

Pyrazinamide

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

Drug Resistance

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

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

Activity *in vitro* and *in vivo*

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

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

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

In vitro testing for *Mycobacterium tuberculosis* isolates
Two standardized *in vitro* susceptibility methods are available for testing isoniazid, rifampin, and pyrazinamide against *Mycobacterium tuberculosis* organisms. The agar proportion method (CDC or CLSI[1] M24-A) utilizes Middlebrook 7H10 medium impregnated with isoniazid at 0.2 and 1.0 mcg/mL and rifampin at 1.0 mcg/mL for the final concentrations of drug. The final concentration for pyrazinamide is 25.0 mcg/mL at pH 5.5. After 3 weeks of incubation MIC_{99} values are calculated by comparing the quantity of organisms growing in the medium containing drug to the control cultures. Mycobacterial growth in the presence of drug ≥1% of the control indicates resistance.

The radiometric broth method employs the BACTEC 460 machine to compare the growth index from untreated control cultures to cultures grown in the presence of 0.2 and 1.0 mcg/mL of isoniazid and 2.0 mcg/mL of rifampin. Strict adherence to the manufacturer's instructions for sample processing and data interpretation is required for this assay. The radiometric broth method has not been approved for the testing of pyrazinamide.

Susceptibility test results obtained by the two different methods can only be compared if the appropriate rifampin or isoniazid concentrations are used for each test method as indicated above. Both test procedures require the use of *Mycobacterium tuberculosis* H37Rv, ATCC 27294, as a control organism.

The clinical relevance of *in vitro* susceptibility test results for mycobacterial species other than *Mycobacterium tuberculosis* using either the radiometric broth method or the proportion method has not been determined.

CLINICAL TRIALS

A total of 250 patients were enrolled in an open label, prospective, randomized, parallel group, active controlled trial for the treatment of pulmonary tuberculosis. There were 241 patients evaluable for efficacy, 123 patients received isoniazid, rifampin, and pyrazinamide as separate tablets and capsules for 56 days, and 118 patients received 4 to 6 RIFATER tablets based on body weight for 56 days. RIFATER tablets and the drugs dosed as separate tablets and capsules were administered based on body weight during the intensive phase of treatment according to the following table.

Dose of Isoniazid, Rifampin, and Pyrazinamide Administered as Separate Drugs			
Patient Weight	**Isoniazid (mg)**	**Rifampin (mg)**	**Pyrazinamide (mg)**

<50 kg	300	450	1500
≥50 kg	300	600	2000

Dose of Isoniazid, Rifampin, and Pyrazinamide Administered as RIFATER				
Patient Weight	**Number of Tablets**	**Isoniazid (mg)**	**Rifampin (mg)**	**Pyrazinamide (mg)**
≤44 kg	4	200	480	1200
45 to 54 kg	5	250	600	1500
≥55 kg	6	300	720	1800

During the continuation phase, both treatment groups received 450 mg of rifampin and 300 mg of isoniazid per day for 4 months if the patient weighed <50 kg or 600 mg of rifampin and 300 mg of isoniazid per day for 4 months if the patient weighed ≥50 kg. Patients were followed for occurrence of relapses for up to 30 months after the end of therapy.

There were no significant differences in the negative bacteriological sputum results (available in a subset of patients) between the two treatments at 2 and 6 months during the trial and during the follow-up period. See table below.

Negative Sputa/No. of Patients (Percent Negative)			
Treatment	**2 Months**	**6 Months**	**Follow-up Period***
RIFATER	91/96 (95%)	100/104 (96%)	99/101 (98%)
Separate†	99/108 (92%)	95/96 (99%)	105/106 (99%)

* The median follow-up time for all the RIFATER patients was 756 days with a range of 42 to 1325 days and 745 days with a range of 50 to 1427 days for the patients dosed with separate tablets and capsules.

† Isoniazid, rifampin, and pyrazinamide dosed as separate tablets and capsules.

For adverse events, see ADVERSE REACTIONS.

INDICATIONS AND USAGE

RIFATER is indicated in the initial phase of the short-course treatment of pulmonary tuberculosis. During this phase, which should last 2 months, RIFATER should be administered on a daily, continuous basis (see DOSAGE AND ADMINISTRATION).

Following the initial phase and treatment with RIFATER, treatment should be continued with rifampin and isoniazid (e.g., RIFAMATE) for at least 4 months. Treatment should be continued for a longer period of time if the patient is still sputum or culture positive, if resistant organisms are present, or if the patient is HIV positive.

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 during the course of treatment. Bacteriologic smears or cultures should be obtained

before the start of therapy to confirm the susceptibility of the organism to rifampin, isoniazid, and pyrazinamide and they should be repeated throughout therapy to monitor response to the treatment. If test results show resistance to any of the components of RIFATER and the patient is not responding to therapy, the drug regimen should be modified.

CONTRAINDICATIONS

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

Rifampin

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

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

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.

WARNINGS

RIFATER is a combination of the three drugs, rifampin, isoniazid, and pyrazinamide. Each of these individual drugs has been associated with liver dysfunction.

Systemic hypersensitivity reactions were reported with all three components of RIFATER (rifampin, isoniazid, and pyrazinamide). 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, such as fever, lymphadenopathy or laboratory abnormalities (including eosinophilia, liver abnormalities) may be present even though rash is not evident. Monitor patients receiving RIFATER for signs and/or symptoms of hypersensitivity reactions. If these signs or symptoms occur, discontinue RIFATER 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 all three components of RIFATER

(rifampin, isoniazid, and pyrazinamide). If symptoms or signs of severe cutaneous adverse reactions develop, discontinue RIFATER immediately and institute appropriate therapy.

Rifampin

Rifampin has been shown to produce liver dysfunction. Fatalities associated with jaundice have occurred in patients with liver disease and in patients taking rifampin with other hepatotoxic agents. Because RIFATER 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 hepatocellular damage occur, RIFATER 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 in 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 amino 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), 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 develop, discontinue RIFATER immediately and institute appropriate therapy.

Isoniazid

(See the boxed WARNING.)

Since RIFATER contains isoniazid, ophthalmologic examinations (including ophthalmoscopy) should be done before treatment is started and periodically thereafter, even without occurrence of visual symptoms.

Severe cutaneous reactions including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (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 report skin rashes or mucosal lesions immediately. Discontinue RIFATER if these reactions occur.

Pyrazinamide

Since RIFATER contains pyrazinamide, patients started on RIFATER should have baseline serum uric acid and liver function determinations. Patients with preexisting liver disease or those patients at increased risk for drug related hepatitis (e.g., alcohol abusers) should be followed closely.

Because it contains pyrazinamide, RIFATER should be discontinued and not be resumed if signs of hepatocellular damage or hyperuricemia accompanied by an acute gouty arthritis appear. If hyperuricemia accompanied by an acute gouty arthritis occurs without liver dysfunction, the patient should be transferred to a regimen not containing pyrazinamide.

PRECAUTIONS

General

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

Rifampin

For treatment of tuberculosis, rifampin is usually administered on a daily basis. Doses of rifampin (>600 mg) given once or twice weekly have resulted in a higher incidence of adverse reactions, including the "flu syndrome" (fever, chills, and malaise); hematopoietic reactions (leukopenia, thrombocytopenia, or acute hemolytic anemia); cutaneous, gastrointestinal, and hepatic reactions; shortness of breath; shock, anaphylaxis, and renal failure. Recent studies indicate that regimens using twice-weekly doses of rifampin 600 mg plus isoniazid 15 mg/kg are much better tolerated.

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 RIFATER, 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.

Pyrazinamide

Pyrazinamide inhibits renal excretion of urates, frequently resulting in hyperuricemia which is usually asymptomatic. If hyperuricemia is accompanied by acute gouty arthritis, RIFATER, because it contains pyrazinamide, should be discontinued.

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 exaggerated response (e.g., headache, sweating, palpitations, flushing, hypotension) to foods containing histamine (e.g., skipjack, tuna, other tropical fish). Tyramine and histamine-containing foods should be avoided in patients receiving RIFATER.

RIFATER, 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.

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

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

Patients should be instructed 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 RIFATER should have baseline measurements of hepatic enzymes, bilirubin, serum creatinine, a complete blood count (CBC) and platelet count (or estimate), and blood uric acid.

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

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 hepatocellular toxicity. Concomitant use of these medications is contraindicated. (See CONTRAINDICATIONS.)

When rifampin is given concomitantly with other hepatotoxic medications such as halothane or isoniazid, the potential for hepatotoxicity is increased. Avoid concomitant use of RIFATER with halothane. Monitor patients receiving RIFATER for hepatotoxicity (See the boxed WARNING.)

Effect of Rifampin on Other Drugs

Induction of Drug Metabolizing Enzymes and Transporter Systems

Drug metabolizing enzymes and transporters affected by rifampin include cytochromes P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, and 3A4, UDP-glucuronyltransferases (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[a]

Drug or Drug Class and Prevention or Management	**Clinical Effect**
Antiretrovirals *Prevention or Management:* Concomitant use is contraindicated (See CONTRAINDICATIONS)	
Atazanavir	Decrease AUC by 72%
Darunavir[b]	Substantial decrease in exposure, which may result in loss of therapeutic effect and development of resistance.
Tipranavir	
Fosamprenavir[c]	Decrease AUC by 82%
Saquinavir	Decrease AUC by 70% Coadministration may result in severe hepatocellular toxicity
Antiretrovirals *Prevention or Management:* Avoid concomitant use	

Zidovudine	Decrease AUC by 47%
Indinavir	Decrease AUC by 92%
Efavirenz	Decrease AUC by 26 %
Hepatitis C Antiviral *Prevention or Management:* Avoid concomitant use	
Daclatasvir	Decrease AUC by 79%
Simeprevir	Decrease AUC by 48%
Sofosbuvir[b]	Decrease AUC by 72% Coadministration of sofosbuvir with rifampin, may decrease sofosbuvir plasma concentrations, leading to reduced therapeutic effect of sofosbuvir.
Telaprevir	Decrease AUC by 92%
Systemic Hormonal Contraceptives *Prevention or Management:* Advise patients to change to non-hormonal methods of birth control during rifampin therapy	
Estrogens	Decrease exposure
Progestins	
Anticonvulsants	
Phenytoin[d]	Decrease exposure[d]
Antiarrhythmics	
Disopyramide	Decrease exposure
Mexiletine	Decrease exposure
Quinidine	Decrease exposure
Propafenone	Decrease AUC by 50%-67%
Tocainide	Decrease exposure
Antiestrogens	
Tamoxifen	Decrease AUC by 86%
Toremifene	Decrease steady state concentrations of toremifene in serum
Antipsychotics	
Haloperidol	Decrease plasma concentrations by 70%
Oral Anticoagulants *Prevention or Management:* Perform prothrombin time daily or as frequently as necessary to establish and maintain the required dose of anticoagulant	
Warfarin	Decrease exposure
Antifungals	

Fluconazole	Decrease AUC by 23%
Itraconazole *Prevention or Management:* Not recommended 2 weeks before and during itraconazole treatment	Decrease exposure
Ketoconazole	Decrease exposure
Beta-blockers	
Metoprolol	Decrease exposure
Propranolol	Decrease exposure
Benzodiazepines	
Diazepam[a,e]	Decrease exposure
Benzodiazepine-related drugs	
Zopiclone	Decrease AUC by 82%
Zolpidem	Decrease AUC by 73%
Calcium Channel Blockers[e]	
Diltiazem	Decrease exposure
Nifedipine[f]	Decrease exposure
Verapamil	Decrease exposure
Corticosteroids[g]	
Prednisolone	Decrease exposure
Cardiac Glycosides	
Digoxin *Prevention or Management:* Measure serum digoxin concentrations before initiating rifampin. Continue monitoring and increase digoxin dose by approximately 20%-40% as necessary.	Decrease exposure
Digitoxin	Decrease exposure
Fluoroquinolones	
Pefloxacin[h]	Decrease exposure
Moxifloxacin[a,d]	Decrease exposure
Oral Hypoglycemic Agents (e.g. sulfonylureas)	
Glyburide	Decrease exposure Rifampin may worsen glucose control of glyburide
Glipizide	Decrease exposure
Immunosuppressive Agents	

Cyclosporine	Decrease exposure	
Tacrolimus *Prevention or Management:* Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when rifampin and tacrolimus are used concomitantly.	Decrease AUC by 56%	
Narcotic Analgesics		
Oxycodone	Decrease AUC by 86%	
Morphine	Decrease exposure	
Selective 5-HT3 Receptor Antagonists		
Ondansetron	Decrease exposure	
Statins Metabolized by CYP3A4		
Simvastatin	Decrease exposure	
Thiazolidinediones		
Rosiglitazone	Decrease AUC by 66%	
Tricyclic Antidepressants		
Nortriptyline[i]	Decrease exposure	
Other Drugs		
Enalapril	Decrease active metabolite exposure	
Chloramphenicol[j]	Decrease exposure	
Clarithromycin	Decrease exposure	
Dapsone	Decrease exposure	
Doxycycline[k]	Decrease exposure	
Irinotecan[l] *Prevention or Management:* Avoid the use of rifampin, strong CYP3A4 inducer, if possible. Substitute non-enzyme inducing therapies at least 2 weeks prior to initiation of irinotecan therapy	Decrease irinotecan and active metabolite exposure	
Levothyroxine	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%

[a] Administered with rifampin 600 mg daily, unless otherwise specified
[b] Rifampin dosage used concomitantly with the drug(s) is not specified in the proposed package insert.
[c] Administered with rifampin 300mg daily
[d] Administered with rifampin 450 mg daily
[e] Administered with rifampin 1200 mg daily
[f] Rifampin 1200 mg administered as a single oral dose 8 hours before administering a single oral dose of nifedipine 10 mg
[g] 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
[h] Administered with rifampin 900 mg daily
[i] A tuberculosis treatment regimen including rifampin (600 mg/day) isoniazid (300 mg/day), pyrazinamide (500 mg 3× 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.
[j] Concomitant use with rifampin in 2 children
[k] Administered with rifampin (10 mg/kg daily)
[l] Administered with an antibiotic regimen including rifampin (450 mg/day), isoniazid (300 mg/day), and streptomycin (0.5 g/day) IM
AUC = area under the time-concentration curve

Effect of Other Drugs on Rifampin

Concomitant use with antacids may reduce the absorption of rifampin which may reduce the efficacy of RIFATER. Administer RIFATER at least 1 hour before the ingestion of antacids.

Concomitant use with probenecid and cotrimoxazole increase the concentration of rifampin which may increase the risk of RIFATER toxicities. Monitor for adverse reactions associated with RIFATER 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 RIFATER 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 RIFATER for hepatotoxicity.

Concomitant use may exaggerate the CNS effects of meperidine (drowsiness), cycloserine (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 drugs metabolized 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, ketoconazole, 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 RIFATER, which also contains rifampin (inducer), on the metabolism of these drugs is unknown.

Other Interactions
Antacid: Concomitant use with antacid may reduce the absorption of isoniazid which may reduce RIFATER efficacy. Administer RIFATER 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 RIFATER 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 RIFATER 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 B_{12}. 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 RIFATER.

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.

Pyrazinamide

Pyrazinamide has been reported to interfere with ACETEST® and KETOSTIX® urine tests to produce a pink-brown color.

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 and 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 C3Hf/DP 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, Escherichia 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. Increased frequency of chromosomal aberrations was observed *in vitro* in lymphocytes obtained from patients treated with combinations of rifampin, isoniazid, and pyrazinamide and combinations of streptomycin, rifampin, isoniazid, and pyrazinamide.

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

Pyrazinamide
Pyrazinamide was not carcinogenic in lifetime bioassays in rats (at doses up to 500 mg/kg, about three times the recommended human dose, based on body surface area comparisons) or mice (at doses up to 2000 mg/kg, about five times the recommended human dose, based on body surface area comparisons).

Pyrazinamide was not mutagenic in the Ames bacterial test, but induced chromosomal aberrations in human lymphocyte cell cultures.

Pregnancy – Teratogenic Effects
Although animal reproduction studies have not been conducted with RIFATER, 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 RIFATER in pregnant women. RIFATER 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). Cleft 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). Imperfect osteogenesis and embryotoxicity were also reported in 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 embryocidal 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).

Pyrazinamide
Animal reproductive studies have not been conducted with pyrazinamide. It is also not known whether pyrazinamide can cause fetal harm when administered to a pregnant woman.

Pregnancy – Non-Teratogenic Effects
When administered during the last few weeks of pregnancy, rifampin can cause post-natal 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
Since rifampin, isoniazid, and pyrazinamide are known to pass into maternal breast milk, a decision should be made whether to discontinue nursing or to discontinue RIFATER, 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 RIFATER 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
Adverse Experiences during the Clinical Trial
Adverse event data reported for the RIFATER and the separate drug treatment groups during the first 2 months of the trial are shown in the table below.

Adverse Events Reported During the Clinical Study		
	Number of Patients with Adverse Events*	
Adverse Events by Body Systems During First 2 Months of Trial	**RIFATER n=122‡**	**Separate† n=123‡**
Cutaneous (rash, erythroderma, erythema, exfoliative dermatitis, Lyell syndrome, urticaria, localized skin rash, diffuse skin rash, pruritus, generalized hypersensitivity)	8 (7%)	21 (17%)
Gastrointestinal (nausea, vomiting, digestive pain, diarrhea)	8 (7%)	14 (11%)
Musculoskeletal (arthralgia, long bones pain, phlebitis, localized joint pain, diffuse joint pain, edema of the legs)	5 (4%)	8 (7%)
Hearing and Vestibular	3 (2%)	6 (5%)

(tinnitus, vertigo, vertigo with loss of equilibrium)		
Liver and Biliary (hepatitis with conjunctival jaundice, hepatitis with deep jaundice)	0 (0%)	2 (2%)
Central and Peripheral Nervous System (sweating, headache, insomnia, diffuse paresthesia of the legs, anxiety, diabetic coma)	5 (4%)	4 (3%)
Total Body (spiking fever, persistent fever)	2 (2%)	4 (3%)
Cardiorespiratory (tightness in chest, coughing, diffuse chest pain, hemoptysis, angina, palpitation, total pneumothorax)	8 (7%)	3 (2%)
Total number of patients with one or more adverse events	29	43

* A given patient may have experienced ≥1 adverse event.
† Isoniazid, rifampin, and pyrazinamide dosed as separate tablets and capsules.
‡ A total of 250 patients (124 RIFATER; 126 separate) were originally enrolled in the study. Five patients (2 RIFATER; 3 separate) were excluded due to admission errors.

No serious adverse events were reported in the patients receiving RIFATER tablets. Three serious adverse events were reported in the patients given isoniazid, rifampin, and pyrazinamide as separate tablets and capsules. The three serious adverse events were two general hypersensitivity reactions and one jaundice reaction.

There were no significant differences between the two treatment groups in standard liver function, renal function, and hematological laboratory test values measured at baseline and after 8 weeks of treatment. As would be expected for these drugs, there were alterations in liver enzymes (SGOT, SGPT) and serum uric acid levels. The adverse reactions reported during therapy with RIFATER are consistent with those described below for the individual components.

Adverse Reactions Reported for Individual Components

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 well-supervised daily therapy. This effect is reversible if the drug is discontinued as soon as purpura occurs. Cerebral hemorrhage and fatalities have been reported when rifampin administration has been continued or resumed after the appearance of purpura.

Rare reports of disseminated intravascular coagulation have been observed.

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

Agranulocytosis has been reported rarely.

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

Psychoses have been rarely reported.

Rare reports of myopathy have also been observed.

Ocular: Visual disturbances have been observed.

Endocrine: Menstrual disturbances have been observed.

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

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

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

Hypersensitivity reactions: Occasionally pruritus, urticaria, rash, pemphigoid reaction, erythema multiforme, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms syndrome (see WARNINGS), vasculitis, eosinophilia, sore mouth, sore tongue and conjunctivitis have been observed.

Anaphylaxis has been reported rarely.

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

Isoniazid

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

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

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

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

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

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

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

Miscellaneous: Rheumatic syndrome and systemic lupus erythematosus-like syndrome.

Pyrazinamide

The principal adverse effect is a hepatic reaction (see WARNINGS). Hepatotoxicity appears to be dose related and may appear at any time during therapy. Pyrazinamide can cause hyperuricemia and gout (see PRECAUTIONS).

Gastrointestinal: GI disturbances including nausea, vomiting, and anorexia have also been reported.

Hematologic and Lymphatic: Thrombocytopenia and sideroblastic anemia with erythroid hyperplasia, vacuolation of erythrocytes and increased serum concentration have occurred rarely with this drug. Adverse effects on blood clotting mechanisms have also been rarely reported.

Other: Mild arthralgia and myalgia have been reported frequently. Hypersensitivity reactions including Drug Reaction with Eosinophilia and Systemic Symptoms syndrome (see WARNINGS), rashes, urticaria, pruritus, and erythema have been reported. Angioedema has been reported rarely. Fever, acne, photosensitivity, porphyria, dysuria, and interstitial nephritis have been reported rarely.

OVERDOSAGE

There is no human experience with RIFATER overdosage.

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 gm rifampin. Fatal acute overdoses in adults have been reported with doses ranging from 14 to 60 gm. Alcohol or a history of alcohol abuse was involved in some of the fatal and nonfatal reports. Nonfatal overdoses in pediatric patients ages 1 to 4 years old of 100 mg/kg for one to two doses have been reported.

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 drug ingestion.

Ingested acutely, 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.

Pyrazinamide

Overdosage experience with pyrazinamide is limited.

Signs and Symptoms

The following signs and symptoms have been seen with each individual component in an overdosage situation.

Rifampin

Nausea, vomiting, abdominal pain, pruritus, headache, and increasing lethargy will probably occur within a short time after rifampin overdosage; unconsciousness may occur when there is severe hepatic disease. Transient increases in liver enzymes and/or bilirubin may occur. Brownish red or orange discoloration of the skin, urine, sweat, saliva, tears, and feces will occur, and its intensity is proportional to the amount ingested.

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

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

Isoniazid

Isoniazid overdosage produces signs and symptoms within 30 minutes to 3 hours. Nausea, vomiting, dizziness, slurring of speech, blurring of vision, and visual hallucinations (including bright colors and strange designs) are among the early manifestations. With marked overdosage, 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.

Pyrazinamide

In one case of pyrazinamide overdosage, abnormal liver function tests developed. These spontaneously reverted to normal when the drug was stopped.

Treatment

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

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

Gastric lavage within the first 2 to 3 hours after ingestion is advised, but it should not be attempted until convulsions are under control. To treat convulsions, administer IV diazepam or short-acting barbiturates, and IV pyridoxine (usually 1 mg/1 mg isoniazid ingested). Following evacuation of gastric contents, the instillation of activated charcoal slurry into the stomach may help absorb any remaining drug from the gastrointestinal tract. Antiemetic medication may be required to control severe nausea and vomiting.

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

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

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

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

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

DOSAGE AND ADMINISTRATION

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

Following the initial phase, treatment should be continued with rifampin and isoniazid (e.g., 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_6) is recommended in the malnourished, 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

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

Patients weighing ≤44 kg – 4 tablets
Patients weighing between 45-54 kg – 5 tablets
Patients weighing ≥55 kg – 6 tablets

Pediatric Patients

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

HOW SUPPLIED

RIFATER tablets are light beige, smooth, round, and shiny sugar-coated tablets imprinted with "RIFATER" in black ink and contain 120 mg rifampin, 50 mg isoniazid, and 300 mg pyrazinamide, and are supplied as:
Bottles of 60 tablets (NDC 0088-0576-41).

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.

REFERENCES

1. Clinical Laboratory Standards Institute. 2003. Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes; Approved Document M24-A.

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