PRODUCT MONOGRAPH

^{Pr}RIFATER®

(rifampin 120 mg, isoniazid 50 mg and pyrazinamide 300 mg)

Manufacturer Standard

Fixed Combination Tablet

Antituberculous Antibiotic

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ACTION AND CLINICAL PHARMACOLOGY

Action

RIFATER (rifampin/isoniazid/pyrazinamide) is an anti-bacterial fixed combination product containing 120 mg rifampin, 50 mg isoniazid and 300 mg pyrazinamide used for the treatment of tuberculosis. Rifampin, isoniazid and pyrazinamide are bactericidal agents active against both intracellular and extracellular tuberculosis organisms.

Rifampin inhibits DNA-dependent RNA polymerase activity in susceptible cells. Specifically, it interacts with bacterial RNA polymerase, but does not inhibit the mammalian enzyme. Cross-resistance to rifampin has only been shown with other rifamycins. Isoniazid kills actively growing tubercle bacilli by inhibition of mycolic acid synthesis. The mechanism of action of pyrazinamide is unknown. *In vitro* and *in vivo* the drug is active only at a slightly acidic pH.

Pharmacokinetics

Pharmacokinetic studies in normal volunteers have shown that the three ingredients in RIFATER have comparable bioavailability whether they are given together as individual dose forms or as RIFATER.

Once daily doses of 4-7 tablets in tubercolosis patients resulted in the following steady state pharmacokinetics.

Table 1: Steady state pharmacokinetic parameters of Isoniazid, Rifampin and Pyrazinamide

	Half-Life (h)	Cmax (mg/L)	Tmax (h)	AUC (mg/L/h)
Isoniazid	2.5	7.6	1.5	34.2
Rifampin	2.0	9.5	2.2	47.9
Pyrazinamide	7.7	41.7	1.8	509.4

INDICATIONS AND CLINICAL USAGE

RIFATER (rifampin/isoniazid/pyrazinamide) 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. When indicated, the addition of other antituberculosis drugs, such as streptomycin and/or ethambutol, should be considered.

Following the initial phase and treatment with RIFATER, treatment should be continued with rifampin and isoniazid 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. Susceptibility tests should be performed in the event of persistent positive cultures during the course of treatment.

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.

RIFATER is not recommended for pediatric use (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections).

CONTRAINDICATIONS

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

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.

RIFATER use is also contraindicated when given concurrently with the combination of saquinavir/ritonavir (See **DRUG INTERACTIONS** section).

WARNINGS

RIFATER (rifampin/isoniazid/pyrazinamide) is a combination of three drugs, each of which has been associated with liver dysfunction.

Clostridium difficile-associated disease

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including RIFATER. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of Clostridium difficile. C. difficile produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against Clostridium difficile. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against Clostridium difficile. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases (see **ADVERSE REACTIONS** section).

Isoniazid

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.

Ophthalmologic examinations (including opthalmoscopy) should be done before isoniazid is started and periodically thereafter, even without occurrence of visual symptoms.

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. Since an increased risk may exist for individuals with liver disease, benefits must be weighed carefully against the risk of further liver damage. Patients with impaired liver function should only be given rifampin in cases of necessity and then with caution and under strict medical supervision. In these patients, careful monitoring of liver function, especially serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) should be carried out prior to therapy and then every two to four weeks during therapy. If signs of hepatocellular damage occur, RIFATER, because it contains rifampin, 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.

High rifampin dose (greater than 600 mg), non-daily and interrupted therapy are associated with a higher incidence of immunological reactions including anaphylaxis; shock and renal failure; hematopoietic reactions (thrombocytopenia, leukopenia or acute haemolytic anemia); “flu syndrome” (fever, chills, headache, dizziness, bone pain and malaise); shortness of breath; cutaneous, gastrointestinal, and hepatic reactions. Patients at increased risk of immunological reactions should be closely monitored. Patients should be advised of the importance of following the prescribed dosage regimen and should be cautioned against interruption of therapy (see **ADVERSE REACTIONS** and **INFORMATION FOR THE CONSUMER** sections).

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

Pyrazinamide

Patients started on pyrazinamide 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 (eg, 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. RIFATER should be used with caution in patients with renal impairment (increased risk of hyperuricemia) or with a history of gout. If hyperuricemia accompanied by an acute gouty arthritis occurs without liver dysfunction, patient should be transferred to a regimen not containing pyrazinamide (see **CONTRAINDICATIONS** section).

PRECAUTIONS

General

RIFATER (rifampin/isoniazid/pyrazinamide) should be used with caution in patients with a history of diabetes mellitus, as management may be more difficult.

A complete blood count (CBC), liver function tests (serum bilirubin, bromsulphalein [BSP] excretion, alkaline phosphatase and serum transaminases), and blood uric acid determinations should be obtained prior to instituting therapy and periodically throughout the course of therapy. Because of a possible transient rise in transaminase and bilirubin values, blood for baseline clinical chemistries should be obtained before RIFATER dosing (see **DRUG INTERACTIONS**, **Drug/laboratory test interactions)**.

RIFATER, because it contains rifampin, may produce a red-orange coloration of the urine, sweat, sputum, and tears. Individuals to be treated should be made aware of these possibilities in order to prevent undue anxiety. Patients should be advised that soft contact lenses may be permanently stained.

Isoniazid:

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

Predisposition to peripheral neuropathy (polyneuritis, presenting as paresthesia, muscle weakness, loss of reflexes, etc) is increased in susceptible populations/conditions such as in adolescence, pregnancy and breastfeeding, elderly, malnutrition, slow acetylator status, alcohol abuse, diabetes, HIV infection, renal failure or seizure disorders. Care should be exercised in the treatment of those predisposed populations/conditions who may also require pyridoxine (vitamin B_6) supplementation with the isoniazid therapy to help prevent neuropathy (see **ADVERSE REACTIONS**, **DOSAGE AND ADMINISTRATION** and **PHARMACOLOGY** sections).

Use of 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.

4. Intravenous drug use is a factor associated with an increased risk of hepatitis.

5. Being a Black or Hispanic woman is a factor associated with an increased risk of hepatitis.

6. Because there is a higher frequency of isoniazid-associated hepatitis among persons older than 35 years of age, a transaminase measurement should be obtained at baseline and at least monthly during therapy in this age group (see **WARNINGS** section).

7. Data suggests that the risk of isoniazid-associated hepatitis may be increased during postpartum period.

8. HIV-infected population has a greater risk of isoniazid-associated adverse reactions. They should be closely monitored by the physician taking into account any underlying conditions, such as hepatic disease.

Rifampin:
Rifampin has been observed to increase the requirements for anticoagulant drugs of the coumarin type. This effect is not observed until the fifth day following initiation of treatment. The decrease in prothrombin time usually lasts between 5 and 7 days. In patients receiving anticoagulants and rifampin concurrently, it is recommended that the prothrombin time be performed daily or as necessary to establish and maintain the required dose of anticoagulant. This is particularly important when rifampin administration is either initiated or withdrawn.

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

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.

Use in pregnancy

Teratogenic Effects:
Animal reproduction studies have not been conducted with RIFATER. It is also not known whether RIFATER can cause fetal harm when administered to a pregnant woman. RIFATER should be given to a pregnant woman only if clearly needed.

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). RIFATER, because it contains isoniazid, should be prescribed during pregnancy only when therapeutically necessary. The benefit of preventive therapy should be weighed against a possible risk to the fetus. Preventive treatment generally should be started after delivery because of the increased risk of tuberculosis for new mothers.

Rifampin

Although rifampin has been reported to cross the placental barrier and appear in cord blood, the effect of rifampin, alone or in combination with other antituberculosis drugs, on the human fetus is not known. An increase in congenital malformations, primarily spina bifida and cleft palate, has been reported in the offspring of rodents given oral doses of 150 to 250 mg/kg/day of rifampin during pregnancy. The possible teratogenic potential in women capable of bearing children should be carefully weighed against the benefits of RIFATER therapy.

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. RIFATER, because it contains pyrazinamide, should be given to a pregnant woman only if clearly needed.

Non-Teratogenic Effects:

It is not known whether RIFATER can affect reproduction capacity.

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.

Use in children

Safety and effectiveness in children have not been established.

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.

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

Rifampin:
There are no known human data on long-term potential for carcinogenicity, mutagenicity, or impairment of fertility. 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. An increase in the incidence of hepatomas in female mice (of a strain known to be particularly susceptible to the spontaneous development of hepatomas) was observed when rifampin was administered in doses two to ten times the average daily human dose for 60 weeks followed by an observation period of 46 weeks. No evidence of carcinogenicity was found in male mice of the same strain, mice of a different strain, or rats under similar experimental conditions.

Rifampin has been reported to possess immunosuppressive potential in rabbits, mice, rats, guinea pigs, human lymphocytes *in vitro,* and humans. Antitumor activity *in vitro* has been shown with rifampin.

There was no evidence of mutagenicity in bacteria, *Drosophila melanogaster,* or mice. An increase in chromatid breaks was noted when whole blood cell cultures were treated with rifampin.

Pyrazinamide:
In lifetime bioassays in rats and mice, pyrazinamide was administered in the diet at concentrations of up to 10,000 ppm. This resulted in estimated daily doses of 2 g/kg for the mouse, or 40 times the maximum human dose, and 0.5 g/kg for the rat, or 10 times the maximum human dose. Pyrazinamide was not carcinogenic in rats or male mice and no conclusion was possible for female mice.

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

Drug interactions

Isoniazid:
Enzyme Inhibition: Isoniazid is known to inhibit certain cytochrome P-450 enzymes. Administration of RIFATER, because it contains isoniazid, with drugs that undergo biotransformation through these metabolic pathways may decrease elimination of coadministered drugs. Therefore, caution should be used when prescribing RIFATER with drugs metabolized by cytochrome P-450. Dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping concomitantly administered RIFATER to maintain optimum therapeutic blood levels.

Isoniazid has been reported to inhibit the metabolism of the following drugs: anticonvulsants (eg, carbamazepine, phenytoin, primidone, valproic acid), benzodiazepines (eg, diazepam),

haloperidol, ketoconazole, theophylline, and warfarin. It may be necessary to adjust the dosages of these drugs if they are given currently with RIFATER because it contains isoniazid. The impact of the competing effects of rifampin and isoniazid on the metabolism of these drugs is unknown.

Other Interactions

Concomitant antacid administration may reduce the absorption of isoniazid. Ingestion with food may also reduce the absorption of isoniazid. Daily doses of isoniazid should be given on an empty stomach at least 1 hour before the ingestion of antacids or food.

Corticosteroids (eg, prednisolone) may decrease the serum concentration of isoniazid by increasing acetylation rate and/or renal clearance. Para-aminosalicylic acid may increase the plasma concentration and elimination half-life of isoniazid by competing for acetylating enzymes.

Pharmacodynamic Interactions

Daily ingestion of alcohol may be associated with a higher incidence of isoniazid hepatitis. Isoniazid, when given concomitantly with rifampin, has been reported to increase the hepatotoxicity of both drugs. Patients receiving both rifampin and isoniazid as in RIFATER should be monitored closely for hepatotoxicity.

In case reports, the CNS effects of meperidine (drowsiness), cycloserine (dizziness, drowsiness), and disulfiram (acute behavioral and coordination changes) may be exaggerated when concomitant isoniazid is given. Concurrent isoniazid and levodopa administration may produce symptoms of excess catecholamine stimulation (agitation, flushing, palpitations) or lack of levodopa effect.

Isoniazid may produce hyperglycemia and lead to loss of glucose control in patients on oral hypoglycemics.

Fast acetylation of isoniazid may produce high concentrations of hydrazine which facilitates deflorination of enflurane. Renal function should be monitored in patients receiving this drug combination.

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 (eg, headache, sweating, palpitations, flushing, hypotension) to foods containing histamine (eg, skipjack, tuna, other tropical fish). Tyramine- and histamine-containing foods should be avoided.

Rifampin :

Enzyme Induction: Rifampin is a potent inducer of certain cytochrome P-450 enzymes. Administration of RIFATER, because it contains rifampin, with drugs that undergo

biotransformation through these metabolic pathways may accelerate elimination of coadministered drugs. Therefore, caution should be used when prescribing RIFATER with drugs metabolized by cytochrome P-450. To maintain optimum therapeutic blood levels, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping concomitantly administered RIFATER.

Examples of drugs metabolized by cytochrome P-450 enzyme are*:* anticonvulsants (eg, phenytoin), antiarrhythmics (eg, disopyramide, mexiletine, quinidine, tocainide, propafenone), antiestrogens (eg tamoxifen, toremifen), antipsychotics (eg haloperidol), oral anticoagulants (eg warfarin), antifungals (eg, fluconazole, itraconazole, ketoconazole), antiretroviral drugs (e.g. zidovudine, saquinavir, indinavir, efavirenz), barbiturates, beta-blockers, benzodiazepines (eg diazepam), benzodiazepine-related drugs (eg zopiclone, zolpidem), calcium channel blockers (eg, diltiazem, nifedipine, verapamil), chloramphenicol, clarithromycin, corticosteroids, cardiac glycoside preparations, clofibrate, oral contraceptives, dapsone, doxycycline, estrogens, gestrinone, oral hypoglycemic agents (sulfonylureas) immunosuppressive agents (e.g. cyclosporine, tacrolimus) irinotecan, levothyroxine, losartan methadone, narcotic analgesics, praziquantel, progestins, quinine, riluzole, selective 5-HT3 receptor antagonists (eg ondansetron), statins metabolized by CYP 3A4, telithromycin, theophylline, thiazolidinediones (e.g.rosiglitazone) and tricyclic antidepressants (eg amitryptyline, nortriptyline). It may be necessary to adjust the dosages of these drugs if they are given concurrently with RIFATER since it contains rifampin.

Other interactions

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

Concurrent use of ketoconazole and rifampin has resulted in decreased serum concentration of both drugs. Concurrent use of rifampin and enalapril has resulted in decreased concentrations of enalaprilat, the active metabolite of enalapril. Dosage adjustments should be made if indicated by the patient's clinical condition.

Concomitant antacid administration may reduce the absorption of rifampin. Daily doses of rifampin should be given at least 1 hour before the ingestion of antacids.

Probenecid and cotrimoxazole have been reported to increase the blood level of rifampin.

When RIFATER is given concomitantly with the combination saquinavir/ritonavir, the potential for hepatotoxicity is increased. Therefore, concomitant use of RIFATER with saquinavir/ritonavir is contraindicated (See **CONTRAINDICATIONS** section).

When rifampin is given concomitantly with either halothane or isoniazid, the potential for hepatotoxicity is increased. The concomitant use of RIFATER and halothane should be avoided. Patients receiving both rifampin and isoniazid as in RIFATER should be monitored closely for

hepatotoxicity (see **WARNINGS** section).

Plasma concentrations of sulfapyridine may be reduced following the concomitant administration of sulfasalazine and rifampin. This finding may be the result of alteration in the colonic bacteria responsible for the reduction of sulfasalazine to sulfapyridine and mesalamine.

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

Drug/laboratory test interactions

Rifampin:
Therapeutic levels of rifampin have been shown to inhibit standard microbiological assays for serum folate and vitamin B_{12}. Therefore, alternate assay methods should be considered.

Transient abnormalities in liver function tests (eg, elevation in serum bilirubin, abnormal bromsulphalein [BSP] excretion, 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. Rifampin can also enhance the metabolism of adrenal hormones.

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

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

ADVERSE REACTIONS

The adverse reactions reported during therapy with RIFATER (rifampin / isoniazid / pyrazinamide) are consistent with reactions described or listed below for the individual components.

Isoniazid
The most frequent reactions are those affecting the nervous system and the liver (see WARNINGS).

Blood and lymphatic system disorders: Agranulocytosis; hemolytic, sideroblastic, or aplastic anemia; thrombocytopenia, eosinophilia. Lymphadenopathy (associated with hypersensitivity reactions).

Gastrointestinal disorders: Nausea, vomiting, epigastric distress, and pancreatitis.

General disorders and administration site conditions: fever (associated with hypersensitivity reactions).

Hepatobiliary disorders: Elevated serum transaminases (ALT, AST), 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.

Immune system disorders: Hypersensitivity reactions including fever, skin eruptions (morbilliform, maculopapular, purpuric, or exfoliative), acne, pemphigus, rash, exfoliative dermatitis, Stevens-Johnson syndrome, systemic lupus erythematosus-like syndrome, lymphadenopathy, vasculitis and anaphylactic reactions.

Metabolism and nutrition disorders: Pyridoxine deficiency, pellagra, hyperglycemia and metabolic acidosis.

Musculoskeletal and connective tissue disorders: Rheumatic syndrome and systemic lupus erythematosus-like syndrome (associated with hypersensitivity reactions).

Nervous system disorders: Peripheral neuropathy (polyneuritis, presenting as paresthesia, muscle weakness, loss of reflexes, etc.) is the most common toxic effect. It is dose-related, occurs most often in those predisposed to neuritis or pyridoxine deficiency (eg, adolescents, pregnant and nursing women, elderly, malnourished, slow acetylators, alcoholics, diabetics, HIV-infected patients, renal failure or seizure disorders), and is usually preceded by paresthesias of the feet and hands. The incidence is higher in "slow inactivators" (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections).

Other neurotoxic effects, which are uncommon with conventional doses, are convulsions (see **SYMPTOMS AND TREATMENT OF OVERDOSAGE** section), toxic encephalopathy, optic neuritis and atrophy, memory impairment, and toxic psychosis.

Reproductive system and breast disorders: gynecomastia.

Skin and subcutaneous tissue disorders: Acne, Stevens-Johnson syndrome, pemphigus, rash, exfoliative dermatitis, and skin eruptions (morbilliform, maculopapular, purpuric, or exfoliative) are generally associated with hypersensitivity reactions.

Vascular disorders: vasculitis (associated with hypersensitivity reactions).

Rifampin

Blood and lymphatic system disorders : Thrombocytopenia with or without purpura 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.

Leukopenia, eosinophilia (associated to hypersensitivity reactions), hemolytic anemia (may be related to hypersensitivity reactions), and decreased hemoglobin have been observed.

Disseminated intravascular coagulation and hemolysis has also been rarely reported.

Agranulocytosis has been reported very rarely.

Endocrine disorders: Menstrual disturbances have been observed. Rare reports of adrenal insufficiency in patients with compromised adrenal function have been observed.

Eye disorders: Visual disturbances and conjunctivitis (associated to hypersensitivity reactions) have been observed.

Gastrointestinal disorders: Heartburn, epigastric distress, anorexia, nausea, vomiting, flatulence, cramps, abdominal discomfort, and diarrhea have been noted in some patients. Occasionally, sore mouth, sore tongue associated to hypersensitivity reactions have been encountered.

General disorders and administration site conditions: Edema of the face and extremities has been reported.

Hepatobiliary disorders: Rarely, hepatitis or a shock-like syndrome with hepatic involvement and abnormal liver function tests has been reported. Transient abnormalities in liver function tests (eg, elevation in serum bilirubin, abnormal bromsulphalein [BSP] excretion, alkaline phosphatase and serum transaminases) have been observed (see **WARNINGS** and **Drug/Laboratory test interactions** sections). A few cases of jaundice with evidence of hepatocellular damage have been reported in patients receiving rifampin. In some of them it was

possible, under careful laboratory control, to resume treatment after an interval without recurrence of abnormalities.

Immune system disorders: Reactions, which usually occurred with intermittent dosage regimens, include "flu" syndrome (such as episodes of fever, chills, headache, dizziness, bone pain and malaise) and immunological reactions (including anaphylaxis) with 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. It rarely occurs during well-supervised daily therapy. Occasionally, pruritus, urticaria, skin rash, pemphigoid reaction, eosinophilia, sore mouth, sore tongue, conjunctivitis, acute hemolytic anemia and acute renal failure (usually due to acute tubular necrosis or to acute interstitial nephritis) have been observed as hypersensitivity reactions.

Infections and infestations: 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 (see **WARNINGS** section).

Investigations: decrease in blood pressure (associated with hypersensitivity reactions).

Musculoskeletal and connective tissue disorders: Rare reports of myopathy have also been observed. Bone pain (may be related to hypersensitivity reactions).

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

Renal and urinary disorders: Elevations in BUN and serum uric acid have been reported. Rarely, hemoglobinuria, hematuria, interstitial nephritis, renal insufficiency, acute tubular necrosis 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.

Respiratory, thoracic and mediastinal disorders: shortness of breath and wheezing are generally associated to hypersensitivity reactions.

Skin and subcutaneous tissue disorders: 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. Erythema multiforme including Stevens-Johnson syndrome, toxic epidermal necrolysis and vasculitis have been reported on rare occasions. Occasionally, pruritus, urticaria, skin rash and pemphigoid reaction are associated to hypersensitivity reactions.

Pyrazinamide

Blood and lymphatic system disorders: Thrombocytopenia with our without purpura 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.

Congenital, familial and genetic disorders: porphyria has been reported rarely.

Gastrointestinal disorders: GI disturbances including aggravation of peptic ulcer, nausea, vomiting, and anorexia have also been reported.

General disorders and administration site condition: fever has been reported rarely. Malaise has also been reported.

Hepatobiliary disorders: The principal adverse effect is a hepatic reaction (see **WARNINGS** section). Hepatotoxicity appears to be dose related, and may appear at any time during therapy. The hepatic reaction can vary from a symptomless abnormality of hepatic cell function (detected only through laboratory liver function tests) through a mild syndrome of fever, malaise and liver tenderness, to more serious reactions as clinical jaundice and rare cases of acute yellow atrophy and death.

Immune system disorders: Hypersensitivity reactions including rashes, urticaria, and pruritus have been reported.

Metabolism and nutrition disorders: Pyrazinamide can cause hyperuricemia and gout (see **PRECAUTIONS** section).

Musculoskeletal and connective tissue disorders: Mild arthralgia and myalgia have been reported frequently.

Renal and urinary disorders: Dysuria and interstitial nephritis have been reported rarely.

Skin and subcutaneous tissue disorders: Very rarely, angioedema has been reported. Acne and photosensitivity have been reported rarely. Occasionally, rashes, erythema, urticaria, and pruritus associated with hypersensitivity reactions have been encountered.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, it is recommended that the regional Poison Control Center be contacted.

General

There is no human experience with RIFATER (rifampin/isoniazid/pyrazinamide) overdosage.

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.

Rifampin:
The minimum acute lethal or toxic dose is not well established. However, non fatal 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 14-60 g, including one case of fatal overdose: a 26-year-old man died after self-administering 60 g of rifampin. Alcohol or a history of alcohol abuse was involved in some of the fatal and non-fatal reports. Nonfatal overdoses in pediatric patients ages 1 to 4 years old of 100 mg/kg for one to two doses has been reported.

Pyrazinamide:
Overdosage experience with pyrazinamide is limited.

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

Isoniazid:
Isoniazid overdosage produces signs and symptoms within 30 minutes to 3 hours after ingestion. Nausea, vomiting, dizziness, slurring of speech, blurring of vision, visual hallucinations (including bright colours 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.

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. 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. 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.

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.

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.

Seizures may be controlled with I.V. diazepam or short-acting barbiturates, and I.V. pyridoxine (dose equivalent to the amount of isoniazid ingested).

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

Gastric lavage as soon as possible within the first 2 to 3 hours after ingestion is advised, but it should not be attempted until convulsions are under control. 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 I.V. sodium bicarbonate at once and repeat as needed, adjusting subsequent dosage on the basis of laboratory findings (eg, serum sodium, pH, etc).

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

Hemodialysis is advised for severe cases; 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.

DOSAGE AND ADMINISTRATION

Adults

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

- Patients weighing 44 kg or less: 4 tablets
- Patients weighing between 45-54 kg: 5 tablets
- Patients weighing 55 kg or greater: 6 tablets

RIFATER (rifampin/isoniazid/pyrazinamide) is recommended in the initial phase of short-course therapy which is usually continued for 2 months. When indicated, the addition of other antituberculosis drugs, such as streptomycin and/or ethambutol, should be considered.

Following the initial phase, treatment should be continued with rifampin and isoniazid 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 those predisposed to neuropathy (eg, adolescents, pregnant and nursing women, elderly, malnourished, slow acetylators, alcoholics, diabetics, HIV-infected patients, renal failure or seizure disorders).

The maximum daily dose for adults, regardless of weight, is:
Rifampin: up to 720 mg/day (see **WARNINGS** section)
Isoniazid: up to 300 mg/day
Pyrazinamide: up to 1800 mg/day

Children

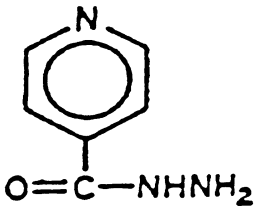
The ratio of the drugs in RIFATER may not be appropriate in children (eg, higher mg/kg doses of isoniazid are usually given in children than adults). RIFATER is therefore not recommended for pediatric use (see **PRECAUTIONS** section).

PHARMACEUTICAL INFORMATION

Drug substances

Isoniazid:

Proper Name ISONIAZID
Chemical Name 4-pyridinecarboxylic acid hydrazide
Structural Formula

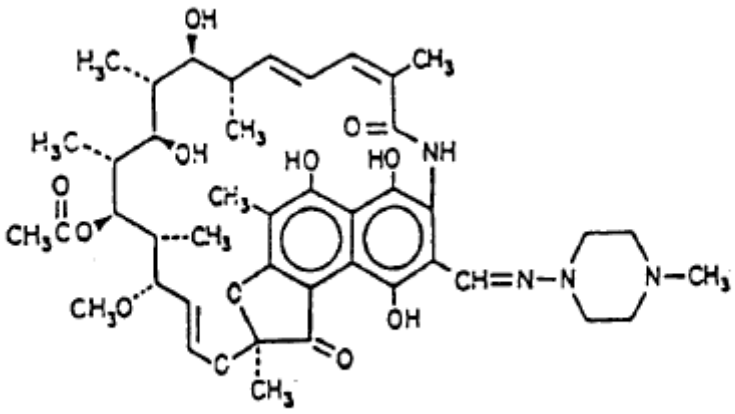


Molecular Formula $C_6H_7N_3O$
Molecular Weight 137.14
Description Colorless or white crystals or white, crystalline powder. Is odourless and is slowly affected by exposure to air and light. Freely soluble in water; sparingly soluble in alcohol; slightly soluble in chloroform; and very slightly soluble in ether. It melts between 170°C-173°C**.** In solution (1 in 10), it has a pH between 6.0 and 7.5.

Rifampin:

Proper Name RIFAMPIN
Chemical Name 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(2*H*)-dione 21-acetate

Structural Formula

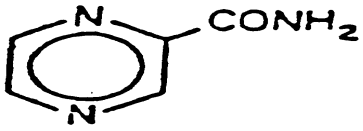


Molecular Formula	$C_{43}H_{58}N_4O_{12}$
Molecular Weight	822.94
Description	Rifampin is a semisynthetic antibiotic derivative of rifamycin B. It is a red-brown crystalline powder very slightly soluble in water, freely soluble in chloroform, and soluble in ethyl acetate and in methanol. It decomposes at 183°-188°C. Rifampin is a zwitterion with pKa 1.7 related to the 4-hydroxy and pKa 7.9 related to the 3-piperazine nitrogen. It has a pH between 4.5 and 6.5 in a suspension (1 in 100).

Pyrazinamide:

Proper Name	PYRAZINAMIDE
Chemical Name	Pyrazinecarboxamide

Structural Formula



Molecular Formula	$C_5H_5N_3O$
Molecular Weight	123.11

Description	White to practically white, odourless or practically odourless, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol, in ether, and in chloroform. It begins to sublime at 60°C and melts between 188°C- 191°C. It has a pKa of 0.5.

Composition

Each RIFATER Tablet contains rifampin 120 mg, isoniazid 50 mg and pyrazinamide 300 mg.

Each tablet also contains as non-medicinal ingredients: acacia, aluminum hydroxide gel, black ink, calcium stearate, carnauba wax, colophony, kaolin, magnesium carbonate, paraffin, povidone, red ferric oxide, silicon dioxide, sodium carboxymethylcellulose, sodium lauryl sulfate, sucrose, talc, titanium dioxide, white beeswax.

STABILITY AND STORAGE DIRECTIONS

Store at controlled room temperature (15-30°C). Protect from moisture.

AVAILABILITY OF DOSAGE FORM

RIFATER Tablets (rifampin 120 mg, isoniazid 50 mg and pyrazinamide 300 mg) are available as light pinky-beige, round, sugar-coated tablets for oral administration. They are supplied in bottles of 60 tablets.

INFORMATION FOR THE PATIENT

Information provided by the prescriber verbally to the patient.

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 (eg, headache, sweating, palpitations, flushing, hypotension) to foods containing histamine (eg, skipjack, tuna, other tropical fish). Tyramine- and histamine-containing foods should be avoided.

Daily consumption of alcohol should be avoided due to increased risk of inflammation of the liver.

RIFATER (rifampin/isoniazid/pyrazinamide), because it contains rifampin, may produce a red-orange coloration of the urine, sweat, sputum, and tears, and the patient should be forewarned of this. Soft contact lenses may be permanently stained.

Patients should be instructed to take RIFATER either one hour before or two hours after a meal.

Concomitant antacid administration may reduce the absorption of isoniazid and rifampin. Antacids should be given at least 1 hour after the daily dose of RIFATER.

Patient should be advised that the reliability of oral contraceptives may be affected; consideration should be given to using alternative contraceptive measures.

Patient should be advised to inform their physician of all relevant medical history (including gout, renal or liver problems) and all concomitant medications taken (including over-the-counter medicines or herbal products).

Patients should be advised to notify their physicians promptly if they experience any of the following adverse reactions: fever, chills, fatigue loss of appetite, malaise, weakness, anaphylaxis including shortness of breath, nausea and vomiting, darkened urine, yellowish discoloration of the skin and eyes, rash or skin reactions, pain or swelling of the joints.

Patients should be advised to inform their doctor promptly if they develop persistent or severe diarrhea.

Compliance with the full course of therapy must be emphasized, and the importance of not missing any doses must be stressed since the incidence of adverse reactions, including hypersensitivity reactions, is increased with interrupted therapy.

Laboratory Tests
A complete blood count (CBC), liver function tests, and blood uric acid determinations should be obtained prior to instituting therapy and periodically throughout the course of therapy. Because of a possible transient rise in transaminase and bilirubin values, blood for baseline clinical chemistries should be obtained before RIFATER dosing.

MICROBIOLOGY

Isoniazid

Isoniazid is a rapidly growing bactericidal for actively dividing *M. tuberculosis* but bacteriostatic against the semi-dormant organisms. Although isoniazid is active against extracellular and intracellular mycobacteria this drug has less sterilizing activity than either rifampin or pyrazinamide. Isoniazid is also active against other species of mycobacteria including *M. kansasii*. The Minimum Inhibitory Concentration (MIC_{90}) of isoniazid for *M. tuberculosis* is 0.05 to 0.2 ug/mL.

Rifampin

Rifampin is bactericidal against a wide range of microorganisms. It is primarily active against rapidly growing, extracellular mycobacteria but due to its lipophilicity and good tissue penetration it also has activity against intracellular organisms and against the slow and intermittently-growing *M. tuberculosis*. It is also active *in vitro* against *M. leprae* and nontuberculosis mycobacteria such as *M. kansasii* and some strains of *M. avian-intracellularae*. The Minimum Inhibitory Concentration (MIC_{90}) of rifampin for *M. tuberculosis* is 0.5 ug/mL.

Pyrazinamide

Pyrazinamide is bactericidal against *M. tuberculosis* in an acid environment, and it is therapeutically effective against persisting, dormant or semi-dormant organisms. It has no activity against other mycobacteria. The Minimum Inhibitory Concentration (MIC_{90}) or pyrazinamide for *M. tuberculosis* is 20 ug/mL at pH 5.5.

Susceptibility testings

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

The Modified Proportion Method proposed by the National Committee for Clinical Laboratory Standards (NCCLS) is recommended to test the susceptibility of *Mycobacterium tuberculosis* to rifampin, isoniazid and pyrazinamide.

In this technique standardized test and control inocula are placed onto drug-containing and drug-free medium and the cultures observed for growth for 3 weeks. At the end of this time, the number of colony-forming units (CFU) growing on the drug-containing medium is compared with the number of CFU on the drug-free medium. *M. tuberculosis* isolates in which growth (CFU) on the drug-containing medium is more than one percent of the CFU growing on the drug-free medium are considered to be clinically resistant to the test antibiotic.

This standardized procedure requires the use of rifampin at a test concentration of 1.0 μg/mL, isoniazid at test concentrations of 0.2 and 1.0 μg/mL, pyrazinamide at a test concentration of 25.0 μg/mL (at pH 5.5) and *M. tuberculosis* ATCC 27294 as a control organism.

PHARMACOLOGY

Rifater

The bioavailability of RIFATER versus individual ingredient products administered concurrently was studied in a single dose, open label, randomized two-way crossover study. Five RIFATER (rifampin/isoniazid/pyrazinamide) Tablets (Treatment A, N=23) versus individual products of RIFADIN 600 mg, isoniazid 250 mg and pyrazinamide 1500 mg (Treatment B, N=24) were administered in healthy male adults. Mean (±SD) pharmacokinetic parameters are summarized in the table no.2 (see also figures 1, 2 and 3).

Table 2: Mean (± SD) pharmacokinetic parameters after a single dose of 5 tablets of Rifater (treatment A) versus Rifadin 600 mg, Isoniazid 250 mg and Pyrazinamide 1500 mg (treatment B) in normal subjects.

Parameter	Cmax (μg/mL)		Half-life (hr)		Apparent Oral Clearance (L/hr)		Bio-avail-ability (5)
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 ± 6.5
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

Renal insufficiency:

The effect of renal impairment on the pharmacokinetics of RIFATER has not been studied.

Hepatic insufficiency:

The effect of hepatic impairment on the pharmacokinetics of RIFATER has not been studied.

Isoniazid

Absorption:

After oral administration, isoniazid is readily absorbed from the gastrointestinal tract and produces peak blood levels within 1 to 2 hours.

Distribution:

It diffuses readily into all body fluids (cerebrospinal, pleural, and ascitic fluids), tissues, organs and excreta (saliva, sputum, and feces). Isoniazid is not substantially bound to plasma proteins. The drug also passes through the placental barrier and into milk in concentrations comparable to those in the plasma.

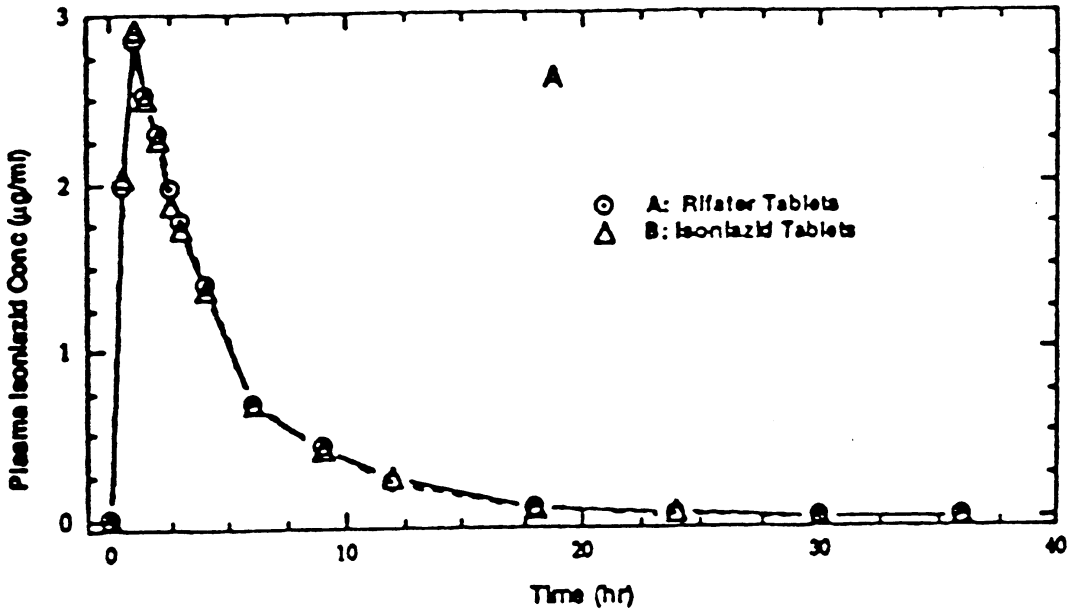
Biological Half-Life:
The plasma half-life of isoniazid in patients with normal renal and hepatic function ranges from 1 to 4 hours, depending on the rate of metabolism.

Excretion:
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 Blacks and Caucasians are "slow inactivators" and the rest are "rapid inactivators"; the majority of Orientals 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.

Figure 1: Mean plasma concentrations of Isoniazid after a single dose of 5 tablets of Rifater versus Isoniazid 250 mg.



Rifampin

Absorption:
Rifampin is readily absorbed from the gastrointestinal tract. Peak blood levels in normal adults and children vary widely from individual to individual. The peak serum level averages 7 μg/mL but may vary from 4 to 32 μg/mL. Absorption of rifampin is reduced when the drug is ingested with food.

Distribution:
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.

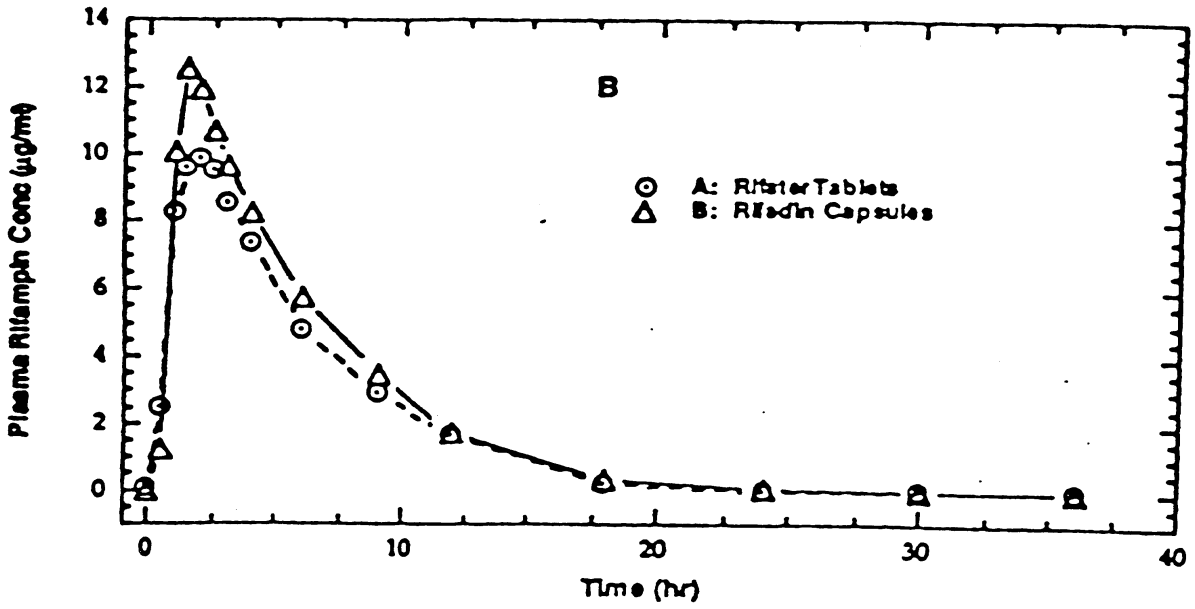
Biological Half-Life:
In normal subjects, the biological half-life of rifampin in serum averages about 3 hours after a 600 mg oral dose, with increases up to 5.1 hours reported after a 900 mg dose. With repeated administration, the half-life decreases and reaches average values of approximately 2 to 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 half-life increased from 3.6 hours in normal subjects 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.

Excretion:
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.

Transplacental Transfer of Rifampin:
Rifampin was administered orally to 20 women at the end of pregnancy in a dose of 300 mg (3.75-5.00 mg/kg) at intervals of 8-12 hours for various lapses of time. Maternal and fetal bloods were collected at parturition. In 5 cases, amniotic fluid was taken. Rifampin (detected by microbiological assay) rapidly crossed both the blood-placental barrier and the chorion, being present in large amounts in fetal blood and amniotic fluid. The maternal blood level of rifampin was higher than the known values for male subjects. It was concluded that the fetus eliminates the drug more slowly than does the mother. Nevertheless, the amount of rifampin found in fetal blood is always less than that of the mother and after repeated dosage, the ratio is about 1:3.

Figure 2: Mean plasma concentrations of Rifampin after a single dose of 5 tablets of Rifater versus Rifadin 600 mg.



Pyrazinamide

Absorption:
Pyrazinamide is well absorbed from the gastrointestinal tract and attains peak plasma concentrations within 2 hours. Plasma concentrations generally range from 30 to 50 µg/mL with doses of 20 to 25 mg/kg.

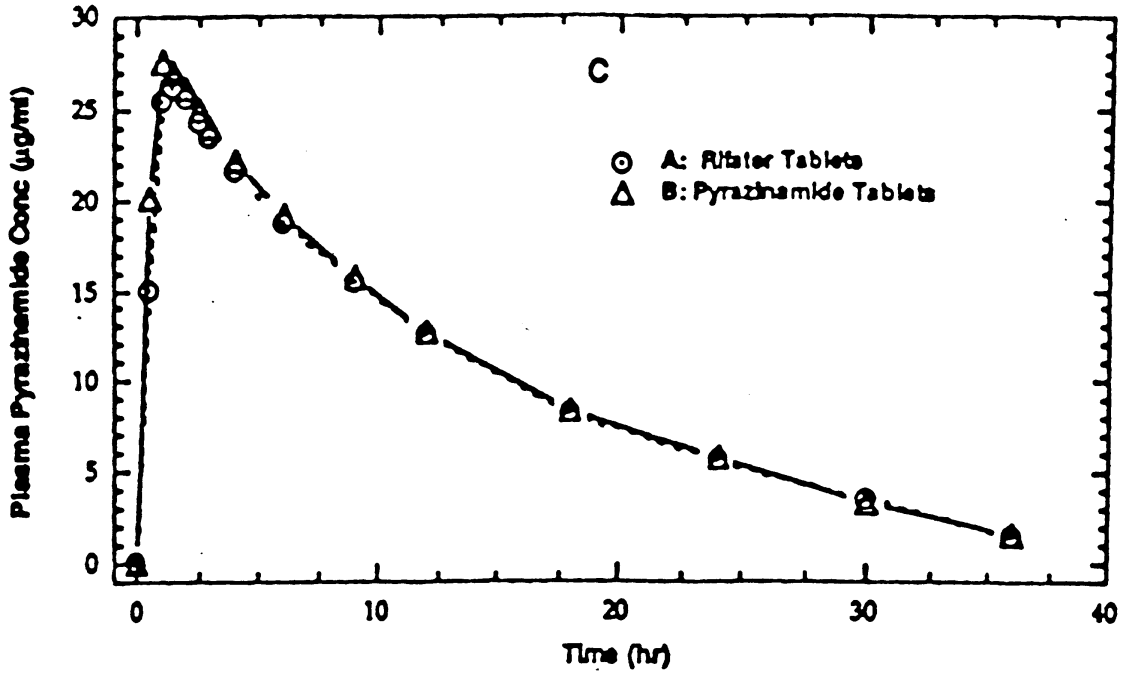
Distribution:
It is widely distributed in body tissues and fluids including the liver, lungs and cerebrospinal fluid (CSF). The CSF concentration is approximately equal to concurrent steady-state plasma concentrations in patients with inflamed meninges.Pyrazinamide is approximately 10% bound to plasma proteins.

Biological Half-Life:
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.

Excretion:
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.

Figure 3: Mean plasma concentrations of Pyrazinamide after a single dose of 5 tablets of Rifater versus Pyrazinamide 1500 mg.



TOXICOLOGY

Toxicology studies for the combination tablet have not been carried out.

Isoniazid
Isoniazid produced lung tumours in mice after oral, intraperitoneal or subcutaneous adminstration. No tumours were detected in oral administration studies in hamsters. Studies completed in the rat were found to be inadequate to evaluate.

Rifampin
There are no known human data on long-term potential for carcinogenicity, mutagenicity, or impairment of fertility. 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. An increase in the incidence of hepatomas in female mice (of a strain known to be particularly susceptible to the spontaneous development of hepatomas) was observed when rifampin was administered in doses two to ten times the average daily human dose for 60 weeks followed by an observation period of 46 weeks. No evidence of carcinogenicity was found in male mice of the same strain, mice of a different strain, or rats under similar experimental conditions.

Rifampin has been reported to possess immunosuppressive potential in rabbits, mice, rats, guinea pigs, human lymphocytes *in vitro*, and humans. Antitumor activity *in vitro* has also been shown with rifampin.

Pyrazinamide
Carcinogenicity studies were carried out on both mice and rats for a 78-week period of drug exposure at 5000 and 10000 ppm followed by a 26-week observation period and compared to an untreated control group. In female mice, a dose-related incidence of lymphoma was observed but due to poor survival and small size of the control group, a clear association of tumour incidence to drug administration could not be made. Pyrazinamide was not carcinogenic for rats or male mice.

MUTAGENICITY

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
In mutagenicity studies, isoniazid did not induce unscheduled DNA synthesis or dominant lethal mutations. Chromosomal aberrations were found in cultured rodent cells but not in human lymphocytes or rodents treated *in vivo*. Isoniazid did not induce gene conversion in yeast but was found to be mutagenic in *Salmonella typhimurium* but not in *E. coli*.

Rifampin
There was no evidence of mutagenicity of rifampin in bacteria, *Drosophila melanogaster*, or mice. An increase in chromatid breaks was noted when whole blood cell cultures were treated with rifampin.

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

REPRODUCTION AND TERATOLOGY

Animal reproduction studies have not been conducted with RIFATER (rifampin/isoniazid/ pyrazinamide). It is also not known whether RIFATER can cause fetal harm when administered to a pregnant woman. RIFATER should be given to a pregnant woman only if clearly needed.

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). Isoniazid should be prescribed during pregnancy only when therapeutically necessary. The benefit of preventive therapy should be weighed against a possible risk to the fetus. Preventive treatment generally should be started after delivery because of the increased risk of tuberculosis for new mothers.

Rifampin
Although rifampin has been reported to cross the placental barrier and appear in cord blood, the effect of rifampin, alone or in combination with other antituberculosis drugs, on the human fetus is not known. An increase in congenital malformations, primarily spina bifida and cleft palate, has been reported in the offspring of rodents given oral doses of 150 to 250 mg/kg/day of rifampin during pregnancy. An increase in the incidence of fetal resorptions, a decrease in fetal numbers and skeletal abnormalities occurred at a dose of 200 mg/kg. The possible teratogenic potential in women capable of bearing children should be carefully weighed against the benefits of therapy.

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. Pyrazinamide should be given to a pregnant woman only if clearly needed.

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