RIFADIN®
(rifampin capsules USP) and
RIFADIN IV
(rifampin for injection USP)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of RIFADIN (rifampin capsules USP) and RIFADIN IV (rifampin for injection USP) and other antibacterial drugs, rifampin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

**DESCRIPTION**

RIFADIN (rifampin capsules USP) for oral administration contains 150 mg or 300 mg rifampin per capsule. The 300 mg and 500 mg capsules also contain, as inactive ingredients: corn starch, D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40, gelatin, magnesium stearate, and titanium dioxide.

RIFADIN IV (rifampin for injection USP) contains rifampin 600 mg, sodium formaldehyde sulfonate 10 mg, and sodium hydroxide to adjust pH to 7.0. It is administered as a 2 mL injection containing 300 mg rifampin per mL.

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 in methanol. Its molecular weight is 822.95 and its chemical name is rifampin or 3-[4-(Methyl-1-piperazinyl)imino]methyl]rifamycin 5,6,9,17,19,21-hexahydroxy-2,4,12,16,18,20,22-trimethyl-8-[N-(4-methyl-1-piperazinyl)formimidoyl]-2,7-(epoxypentadeca[1,11,13]

Plasma concentrations after the 600 mg dose, which were disproportionately higher (up to 400% greater than expected) after the 300 mg dose, indicated that the elimination of larger doses was not as rapid. After repeated once-a-day infusions (3-hr duration) of 600 mg in patients (n=5) for 7 days, concentrations of IV rifampin decreased from 5.81±3.38 mcg/mL 8 hours after the infusion on day 1 to 2.6±1.88 mcg/mL 8 hours after the infusion on day 7. 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, diffuses freely into tissues.

Rifampin is rapidly eliminated in the bile and undergoes progressive enterohepatic recirculation and deacetylation to the primary metabolite, 25-desacetyl-rifampin. This metabolite is microbiologically active. Less than 30% of the dose is excreted in the urine as rifampin or metabolites. Serum concentrations do not differ in patients with renal failure at the usual dose of 300 mg, and consequently, no dosage adjustment is required.

**Pediatrics**

**Oral Administration**

In one study, pediatric patients 6 to 58 months old were given rifampin suspended in simple syrup or as dry powder mixed with apple juice 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 preenalinal drug suspension and the apple juice mixture, respectively. After the administration of either preparation, the t1/2 of rifampin averaged 2.8 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.

**Intravenous Administration**

In pediatric patients 0.25 to 12.8 years old (n=12), the mean peak serum concentration of rifampin at the end of a 3-minute infusion of approximately 300 mg/m2 was 25.1±3.1 mcg/mL, individual peak concentrations 1 to 4 days after initiation of therapy ranged from 11.7 to 41.5 mcg/mL, individual peak concentrations of 5 to 14 days after initiation of therapy were 13.6 to 37.4 mcg/mL. The individual serum half-life of rifampin changed from 1.04 to 3.61 hours early in therapy to 1.71 to 3.19 hours 5 to 14 days after therapy was initiated.

**Microbiology**

**Mechanism of Action**

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.

**Resistance**

Organisms resistant to rifampin are likely to be resistant to other rifamycins.

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

**Activity in vitro and in vivo**

Rifampin has bactericidal activity in vitro against slow and intermittently growing M. tuberculosis organisms. Rifampin has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section.

**Aerobic Gram-Negative Microorganisms:**

- Neisseria meningitidis
- Other Microorganisms:
  - Mycobacterium tuberculosis

The following in vitro data are available, but their clinical significance is unknown.

Rifampin exhibits in vitro activity against most strains of the following microorganisms; however, the safety and effectiveness of rifampin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

**Aerobic Gram-Positive Microorganisms:**

- Staphylococcus aureus (including Methicillin-Resistant S aureus/MRSA)
- Staphylococcus epidermidis
- Aerobic Gram-Negative Microorganisms:
  - Haemophilus influenzae
  - Other Microorganisms:
  - Mycobacterium leprae

- β-lactamase production should have no effect on rifampin activity.

**Susceptibility Testing**

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

**INDICATIONS AND USAGE**

In the treatment of both tuberculosis and the meningococcal carrier state, the small number of resistant cells present within large populations of susceptible cells can rapidly become the predominant type. Bacteriologic cultures should be obtained before the start of therapy and repeated throughout therapy to monitor the response to treatment. Since resistance can emerge rapidly, susceptibility tests should be performed in the event of persistent positive cultures during the course of treatment. If test results show resistance to rifampin and the patient is not responding to therapy, the drug regimen should be modified.

**Tuberculosis**

Rifampin is indicated in the treatment of all forms of tuberculosis.

A three-drug regimen consisting of rifampin, isoniazid, and pyrazinamide (e.g., RIFATER®) is recommended. After the initial phase of short-course therapy which is usually continued for 2 months. The Advisory Council for the Elimination of Tuberculosis, the American Thoracic Society, and Centers for Disease Control and Prevention recommend that either streptomycin or ethambutol be added as a fourth drug in a regimen containing isoniazid (INH), rifampin, and pyrazinamide for initial treatment of tuberculosis unless the likelihood of INH 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.

**CLINICAL PHARMACOLOGY**

**Oral Administration**

Rifampin is readily absorbed from the gastrointestinal tract. Peak serum concentrations 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 concentration 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.

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, diffuses freely into tissues.

In healthy adults, the mean biological half-life of rifampin in serum averages 3.3 to 6.6 hours after a 600 mg oral dose, with increases up to 5.6 to 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 after doses not exceeding 800 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 500 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 to 50 mL/min, less than 30 mL/min, and in anuric patients, respectively. Refer to the WARNINGS section for information regarding patients with hepatic insufficiency.

After absorption, rifampin is rapidly eliminated in the bile, and an enterohepatic circulation ensues. During this process, rifampin undergoes progressive deacetylation so that nearly all the drug in the bile is in this form in about 6 hours. This metabolite has antibacterial activity. Intestinal reabsorption is reduced by deacetylation, and elimination is facilitated. Up to 30% of a dose is excreted in the urine, with about half of this being unchanged drug.

**Intravenous Administration**

After intravenous administration of a 300 or 600 mg dose of rifampin infused over 30 minutes to healthy adults, the peak plasma concentrations were 9.0±3.0 and 17.5±5.0 mcg/mL, respectively. Total body clearances after the 300 and 600 mg IV doses were 0.19±0.06 and 0.14±0.03 L/hr/kg, respectively. Volumes of distribution at steady state were 0.68±0.14 and 0.64±0.11 L/kg for the 300 and 600 mg IV doses, respectively. After intravenous administration of 300 or 600 mg doses, rifampin plasma concentrations in these volunteers remained detectable for 8 and 12 hours, respectively (see Table).
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.

RIFADIN IV is indicated for the initial treatment and retreatment of tuberculosis when the drug cannot be taken by mouth.

**Meningococcal Carriers**

Rifampin is indicated for the treatment of asymptomatic carriers of Neisseria meningitidis to eliminate meningococci from the nasopharynx. Rifampin is not indicated for the treatment of meningococcal infection because of the possibility of the rapid emergence of resistant organisms. (See WARNINGS.)

Rifampin should not be used indiscriminately, and, therefore, diagnostic laboratory procedures, including serotyping and susceptibility testing, should be performed for confirmation of the diagnosis and that the usefulness of rifampin in the treatment of asymptomatic meningococcal carriers is preserved, the drug should be used only when the risk of meningococcal disease is high.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of rifampin and other antibacterial drugs, rifampin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

**CONTRAINDICATIONS**

RIFADIN is contraindicated in patients with a history of hypersensitivity to rifampin or any of the components, or to any of the rifamycins. (See WARNINGS.)

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 azathioprine, mercaptopurine, or 6-mercaptopurine due to the potential of rifampin to substantially decrease the plasma concentrations of these 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 of drug-resistant schistosomiasis, other antischistosomal agents should be used. 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 therapy.

**WARNINGS**

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. Patients with impaired liver function should be given rifampin only in cases in which the benefits clearly outweigh the risks. In medical supervision of such patients, careful monitoring of liver function, especially SGPT/ALT and SGOT/AST, should be carried out prior to therapy and then every 2 to 4 weeks during therapy. If signs of hepatocellular damage occur, rifampin should be discontinued. Cases of fulminant hepatic failure have been reported with rifampin therapy. Patients should be instructed to contact their physician immediately if they experience symptoms such as itching, weight loss, loss of appetite, nausea, vomiting, abdominal pain, yellowing of eyes or skin, or dark urine. If cholestatic jaundice is confirmed, RIFADIN should be discontinued.

Cases of severe cholestasis have been reported with rifampin therapy. Patients should be instructed to contact their physician immediately if they experience symptoms such as itching, weight loss, loss of appetite, nausea, vomiting, abdominal pain, yellowing of eyes or skin, or dark urine. If cholestasis is confirmed, RIFADIN should be discontinued. 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 showed 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.

The possibility of rapid emergence of resistant meningococci restricts the use of RIFADIN to short-term treatment of the asymptomatic carrier state. RIFADIN is not to be used for the treatment of meningococcal disease.

Systemic hypersensitivity reactions were reported with RIFADIN administration. 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, dysphagia), 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 RIFADIN for signs and symptoms of hypersensitivity reactions. If these signs or symptoms occur, discontinue RIFADIN and institute supportive treatment.

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 RIFADIN immediately and institute appropriate therapy.

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

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

**PRECAUTIONS**

**General**

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

Prescribing rifampin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

For the treatment of tuberculosis, rifampin is usually administered on a daily basis. Doses of rifampin greater than 600 mg given once or twice weekly have resulted in a higher incidence of adverse reactions, including the “flu syndrome” (fever, chills, and malaise), hematopoietic depression, hepatic reactions, 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. 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.

**RIFADIN IV**

For intravenous infusion only. Must not be administered by intramuscular or subcutaneous route. Avoid extravasation during injection: local irritation and inflammation due to extravascular infiltration of the drug can be observed. If these occur, the infusion should be discontinued and restarted at another site.

**Information for Patients**

Patients should be counseled that antibacterial drugs such as rifampin should only be used to treat or prevent bacterial infections. They do not treat viral infections (e.g., the common cold).

If rifampin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may decrease the effectiveness of the immediate treatment and increase the likelihood that bacteria will develop resistance and will not be treatable by rifampin or other antibacterial drugs in the future.

Patients should be told that rifampin may produce a discoloration (yellow, orange, red, brown) of the teeth, urine, sweat, 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 may therefore decrease the 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 rifampin either 1 hour before or 2 hours after a meal with a full glass of water.

The patient should be instructed to notify their physician immediately if they experience any of the following: rash, 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, and 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 rifampin should have baseline measurements of hepatic enzymes, bilirubin, serum creatinine, a complete blood count, and a platelet count (or estimate). Baseline tests are unnecessary in pediatric patients unless a complicating condition is known or clinically suspected.

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**

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 rash, fever, and malaise. Following the discontinuation of rifampin, rash, fever, and malaise resolved. Therefore, rifampin may accelerate the metabolism and reduce the activity of certain coadministered drugs, and has the potential to perpetuate clinically important drug-drug interactions against many drugs and across many drug classes (Table 1).
Table 1 summarizes the effect of rifampin on other drugs or drug classes. Adjust dosages of concomitant drugs based on approved drug labeling and if applicable, therapeutic drug monitoring, unless otherwise specified.

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

<table>
<thead>
<tr>
<th>Drug or Drug Class and Prevention or Management</th>
<th>Clinical Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiretrovirals</strong></td>
<td></td>
</tr>
<tr>
<td>Prevention or Management: Concomitant use is contraindicated (See CONTRAINDICATIONS)</td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Decrease AUC by 72%</td>
</tr>
<tr>
<td>Darunavir†</td>
<td>Substantial decrease in exposure, which may result in loss of therapeutic effect and development of resistance.</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>Decrease AUC by 82%</td>
</tr>
<tr>
<td>Fosamprenavir†</td>
<td>Decrease AUC by 70% Coadministration may result in severe hepatocellular toxicity</td>
</tr>
<tr>
<td>Saquinavir</td>
<td></td>
</tr>
</tbody>
</table>

**Antiretrovirals** Prevention or Management: Avoid concomitant use

- Zidovudine                                    Decrease AUC by 47%
- Indinavir                                     Decrease AUC by 92%
- Elaviren                                      Decrease AUC by 26%

**Hepatitis C Antiviral** Prevention or Management: Avoid concomitant use

- Daclatasvir                                    Decrease AUC by 79%
- Simeprevir                                     Decrease AUC by 48%
- Sofosbuvir†                                    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                                     Decrease exposure

**Anticonvulsants**

- Phenytoin§                                     Decrease exposure§

**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
- Ketoconazole                                   Decrease exposure

**Beta-blockers**

- Metoprolol                                     Decrease exposure
- Propranolol                                    Decrease exposure

**Benzodiazepines**

- Diazepam§                                     Decrease exposure

**Benzodiazepine-related drugs**

- Zopiclone                                     Decrease AUC by 82%
- Zolpidem                                      Decrease AUC by 73%

**Calcium Channel Blockers**

- Diltiazem                                      Decrease exposure

**Fluoroquinolones**

- Pefloxacin†                                   Decrease exposure
- Moxifloxacin†‡                                 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.

**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†                                 Decrease exposure

**Other Drugs**

- Enalapril                                      Decrease active metabolite exposure
- Chloramphenicol®†                               Decrease exposure
- Clarithromycin                                 Decrease exposure
- Dapsone                                        Decrease exposure

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Table 1: Drug Interactions with Rifampin that Affect Concomitant Drug Concentrations (continued)
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<thead>
<tr>
<th>Drug or Drug Class and Prevention or Management</th>
<th>Clinical Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doxycline</strong></td>
<td>Decrease exposure</td>
</tr>
<tr>
<td><strong>Irinotecan</strong></td>
<td>Decrease irinotecan and active metabolite exposure</td>
</tr>
<tr>
<td><strong>Levotyroxine</strong></td>
<td>Decrease exposure</td>
</tr>
<tr>
<td><strong>Losartan</strong></td>
<td>Parent Decrease AUC by 30%</td>
</tr>
<tr>
<td></td>
<td>Active metabolite (E3174) Decrease AUC by 40%</td>
</tr>
<tr>
<td><strong>Methadone</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Praziquantel</strong></td>
<td>Decrease plasma praziquantel concentrations to undetectable levels.</td>
</tr>
<tr>
<td><strong>Quinine</strong></td>
<td>Decrease AUC by 75%–85%</td>
</tr>
<tr>
<td><strong>Teliromycin</strong></td>
<td>Decrease AUC by 86%</td>
</tr>
<tr>
<td><strong>Theophylline</strong></td>
<td>Decrease exposure by 20% to 40%</td>
</tr>
</tbody>
</table>

AUC = area under the time-concentration curve

*Administered with rifampin 300 mg daily
*Administered with rifampin 450 mg daily
*Administered with rifampin 1200 mg daily
*Rifampin 1200 mg administered as a single oral dose 8 hours before administering a single oral dose of nifedipine 10 mg
*Numbers in the literature describe a decrease in glucocorticoid effect when used concomitantly with rifampin. The literature contains reports of acute adrenal crisis or adrenal insufficiency induced by the combination of rifampin-isoniazid-ethambutol or rifampin-isoniazid in patients with Addison’s disease
*Administered with rifampin 300 mg daily
*Administered with rifampin 1200 mg daily
*Rifampin 1200 mg administered as a single oral dose 8 hours before administering a single oral dose of nifedipine 10 mg
*Number of 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
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Effect of other drugs on rifampin

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. Concomitant use with probenecid and cotrimoxazole increase the concentration of rifampin which may increase the risk of RIFADIN toxicities. Monitor for adverse reactions associated with RIFADIN during concomitant administration.

**Other Interactions**

**Atovaquone**

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

**Drug/Laboratory Interactions**

Cross-reactivity and false-positive urine screening tests for opiates have been reported in patients receiving rifampin when using the KIMS (Kinetic Interaction of Microorganisms with Solution) method (e.g., Abscreen 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 folate and vitamin B12. Thus, alternate 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 rifampin.

**Carcinogenesis, Mutagenesis, 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. Hepatomas were increased in female (C3H/DB) 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 C3H/DB 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, Dro sophila 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 lymphocytes obtained from patients treated with combinations of rifampin, isoniazid, and pyrazinamide and combinations of streptomycin, rifampin, isoniazid, and pyrazinamide.

**Pregnancy–Teratogenic Effects**

Rifampin has been shown to be teratogenic in rodents. 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 litters of pregnant mice treated with 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 human dose based on body surface area comparisons). There are no adequate and well-controlled studies of RIFADIN in pregnant women. Rifampin has been reported to cross the placental barrier and appear in cord blood. RIFADIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Pregnancy–Non-Teratogenic Effects**

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

**Nursing Mothers**

Because of the potential for tumorigenicity shown for rifampin in animal studies, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use**

See CLINICAL PHARMACOLOGY–Pediatrics; see also DOSAGE AND ADMINISTRATION.

**Geriatric Use**

Clinical studies of RIFADIN 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 in elderly patients. (See WARNINGS.)

**ADVERSE REACTIONS**

### 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. Cholestasis 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, decreased hemoglobin, bleeding, and vitamin K–dependent coagulation disorders (abnormal prolongation of prothrombin time or low vitamin K–dependent coagulation factors) have been observed. Agranulocytosis has been reported very 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**

Mental 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, intermittent nephritis, acute tubular necrosis, renal insufficiency, and asymptomatic proteinuria have been noted. These are generally considered to be hypersensitivity reactions. They usually occur during intermittent therapy or when treatment is resumed following intermittent or accidental interruption of a daily dosage regimen, and are less likely to occur 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.
Meningococcal Carriers

Adults: For adults, it is recommended that 600 mg rifampin be administered twice daily for two days.

Pediatric Patients: Pediatric patients 1 month of age or older: 10 mg/kg (not to exceed 600 mg per dose) every 12 hours for two days.

Pediatric patients under 1 month of age: 5 mg/kg every 12 hours for two days.

Preparation of Extemporaneous Oral Suspension

For pediatric and adult patients in whom capsule swallowing is difficult or where lower doses are needed, a liquid suspension may be prepared as follows:

RIFADIN 1% w/v suspension (10 mg/mL) can be compounded using one of four syrups—Simple Syrup (SF), Simple Syrup (Humco Laboratories), SyrPalt® Syrup (Emerson Laboratories), or Raspberry Syrup (Humco Laboratories).

1. Empty the contents of four RIFADIN 300 mg capsules or eight RIFADIN 150 mg capsules onto a piece of weighing paper.

2. If necessary, gently crush the capsule contents with a spatula to produce a fine powder.

3. Transfer the rifampin powder blend to a 4-ounce amber glass or plastic (high density polyethylene [HDPE], polypropylene, or polycarbonate) prescription bottle.

4. Rinse the paper and spatula with 20 mL of one of the above-mentioned syrups, and add the rinse to the bottle. Shake vigorously.

5. Add 100 mL of syrup to the bottle and shake vigorously.

This compounding procedure results in a 1% w/v suspension containing 10 mg rifampin/mL. Stability studies indicate that the suspension is stable when stored at room temperature (25±3°C) or in a refrigerator (2–8°C) for four weeks. This extemporaneously prepared suspension must be shaken well prior to administration.

HOW SUPPLIED

150 mg maroon and scarlet capsules imprinted “RIFADIN 150.” Bottles of 30 (NDC 0068-0510-30) 300 mg maroon and scarlet capsules imprinted “RIFADIN 300.” Bottles of 90 (NDC 0068-0597-90)

Storage: Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Keep tightly closed. Store in a dry place. Avoid excessive heat.

RIFADIN IV (rifampin for injection USP) is available in sterile glass vials containing 600 mg rifampin (NDC 0068-0597-01).

Storage: Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Avoid excessive heat (temperatures above 40°C or 104°F). Protect from light.

REFERENCES


Rifadin capsules are manufactured for:

sanofi-aventis U.S. LLC

Bridgewater, NJ 08807

A SANOFI COMPANY

Rifadin IV (rifampin for injection USP) is manufactured by:

sanofi-aventis U.S. LLC

Bridgewater, NJ 08807

A SANOFI COMPANY

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Preparation of Solution for IV Infusion

Reconstitute the lyophilized powder by transferring 10 mL of sterile water for injection to a vial containing 600 mg of rifampin for injection. Swirl vial gently to completely dissolve the antibiotic. The reconstituted solution contains 60 mg rifampin per mL and is stable at room temperature for up to 30 hours. Prior to administration, withdraw from the reconstituted solution a volume equivalent to the amount of rifampin calculated to be administered and add to 500 mL of infusion medium. Mix well and infuse at a rate allowing for complete infusion within 3 hours. Alternatively, the amount of rifampin calculated to be administered may be added to 100 mL of infusion medium and infused in 30 minutes. Dilutions in dextrose 5% for injection (dextrose 5%) are stable at room temperature for up to 8 hours and should be prepared and used within this time. Precipitation of rifampin from the infusion solution may occur beyond this time. Dilutions in normal saline are stable at room temperature for up to 6 hours and should be prepared and used within this time. Other infusion solutions are not recommended.

Incompatibilities

Physical incompatibility (precipitate) was observed with undiluted (5 mg/mL) and diluted (1 mg/mL in normal saline) diethylaminochlorohydrochloride and rifampin (6 mg/mL in normal saline) during simulated Y-site administration.