

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

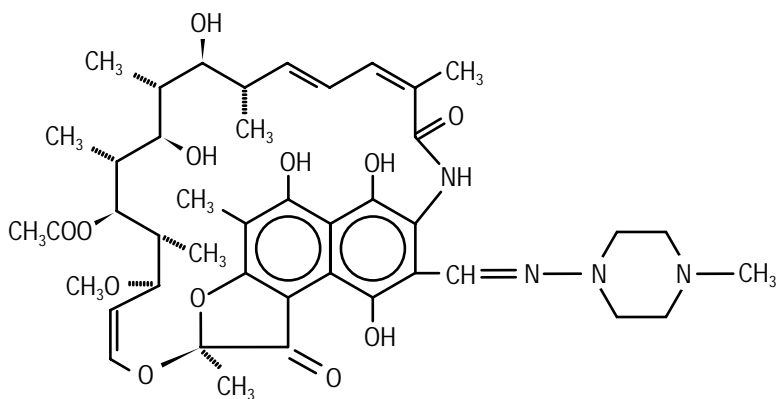
RIFADIN (rifampin capsules USP) for oral administration contain 150 mg or 300 mg rifampin per capsule. The 150 mg and 300 mg capsules also contain, as inactive ingredients: corn starch, D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40, gelatin, magnesium stearate, and titanium dioxide.

RIFADIN IV (rifampin for injection USP) contains rifampin 600 mg, sodium formaldehyde sulfoxylate 10 mg, and sodium hydroxide to adjust pH.

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 formula is $C_{43}H_{58}N_4O_{12}$. The chemical name for rifampin is either:

3-[[[4-Methyl-1-piperaziny]imino]methyl]rifamycin
or
5,6,9,17,19,21-hexahydroxy-23-methoxy-2,4,12,16,20,22-
heptamethyl-8-[N-(4-methyl-1-piperaziny)formimidoyl]-2,7-(epoxypentadeca
[1,11,13]trienimino)naphtho[2,1-*b*]furan-1,11(2H)-dione 21-acetate.

Its structural formula is:



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 3.35 ± 0.66 hours after a 600 mg oral dose, with increases up to 5.08 ± 2.45 hours reported after a 900 mg dose. With repeated administration, the half-life decreases and reaches average values of approximately 2 to 3 hours. The half-life does not differ in patients with renal failure at doses not exceeding 600 mg daily, and consequently, no dosage adjustment is required. Following a single 900 mg oral dose of rifampin in patients with varying degrees of renal insufficiency, the mean half-life increased from 3.6 hours in healthy adults to 5.0, 7.3, and 11.0 hours in patients with glomerular filtration rates of 30 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.

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 is microbiologically active. 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 male volunteers (n=12), mean 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 0.66 ± 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).

Plasma Concentrations (mean \pm standard deviation, mcg/mL)						
Rifampin Dosage IV	30 min	1 hr	2 hr	4 hr	8 hr	12 hr
300 mg	8.9 \pm 2.9	4.9 \pm 1.3	4.0 \pm 1.3	2.5 \pm 1.0	1.1 \pm 0.6	<0.4
600 mg	17.4 \pm 5.1	11.7 \pm 2.8	9.4 \pm 2.3	6.4 \pm 1.7	3.5 \pm 1.4	1.2 \pm 0.6

Plasma concentrations after the 600 mg dose, which were disproportionately higher (up to 30% greater than expected) than those found 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 circulation 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 a studied 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 applesauce at a dose of 10 mg/kg body weight. Peak serum concentrations of 10.7 ± 3.7 and 11.5 ± 5.1 mcg/mL were obtained 1 hour after preprandial ingestion of the drug suspension and the applesauce mixture, respectively. After the administration of either preparation, the $t_{1/2}$ of rifampin averaged 2.9 hours. It should be noted that in other studies in pediatric populations, at doses of 10 mg/kg body weight, mean peak serum concentrations of 3.5 mcg/mL to 15 mcg/mL have been reported.

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 30 minute infusion of approximately 300 mg/m² was 25.9 ± 1.3 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 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 3.81 hours early in therapy to 1.17 to 3.19 hours 5 to 14 days after therapy was initiated.

Microbiology

Rifampin inhibits DNA-dependent RNA polymerase activity in susceptible cells. Specifically, it interacts with bacterial RNA polymerase but does not inhibit the mammalian enzyme. Rifampin at therapeutic levels has demonstrated bactericidal activity against both intracellular and extracellular *Mycobacterium tuberculosis* organisms.

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

Rifampin has bactericidal activity against slow and intermittently growing *M tuberculosis* organisms. It also has significant activity against *Neisseria meningitidis* isolates (see INDICATIONS AND USAGE).

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.

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 Tests

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

In vitro testing for *Mycobacterium tuberculosis* isolates:

Two standardized in vitro susceptibility methods are available for testing rifampin against *M. tuberculosis* organisms. The agar proportion method (CDC or NCCLS⁽¹⁾ M24-P) utilizes Middlebrook 7H10 medium impregnated with rifampin at a final concentration of 1.0 mcg/mL to determine drug resistance. After three weeks of incubation MIC₉₉ values are calculated by comparing the quantity of organisms growing in the medium containing drug to the control

cultures. Mycobacterial growth in the presence of drug, of at least 1% of the growth in the control culture, indicates resistance.

The radiometric broth method employs the BACTEC 460 machine to compare the growth index from untreated control cultures to cultures grown in the presence of 2.0 mcg/mL of rifampin. Strict adherence to the manufacturer's instructions for sample processing and data interpretation is required for this assay.

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

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

In vitro testing for *Neisseria meningitidis* isolates:

Dilution Techniques: Quantitative methods that are used to determine minimum inhibitory concentrations provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method^{2,4} (broth, agar, or microdilution) or equivalent with rifampin powder. The MIC values obtained should be interpreted according to the following criteria for *Neisseria meningitidis*:

<u>MIC (mcg/mL)</u>	<u>Interpretation</u>
≤ 1	(S) Susceptible
2	(I) Intermediate
≥ 4	(R) Resistant

A report of "susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in the blood. A report of "intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where the maximum acceptable dose of drug can be used. This category also provides a buffer zone that prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of "resistant" indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and that other therapy should be selected.

Measurement of MIC or minimum bactericidal concentrations (MBC) and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See CLINICAL PHARMACOLOGY section for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product.)

Standardized susceptibility test procedures require the use of laboratory control microorganisms. The use of these microorganisms does not imply clinical efficacy (see INDICATIONS AND

USAGE); they are used to control the technical aspects of the laboratory procedures. Standard rifampin powder should give the following MIC values:

<u>Microorganism</u>		<u>MIC (mcg/mL)</u>
<i>Staphylococcus aureus</i>	ATCC 29213	0.008 - 0.06
<i>Enterococcus faecalis</i>	ATCC 29212	1 - 4
<i>Escherichia coli</i>	ATCC 25922	8 - 32
<i>Pseudomonas aeruginosa</i>	ATCC 27853	32 - 64
<i>Haemophilus influenzae</i>	ATCC 49247	0.25 - 1

Diffusion Techniques: Quantitative methods that require measurement of zone diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure^{3,4} that has been recommended for use with disks to test the susceptibility of microorganisms to rifampin uses the 5 mcg rifampin disk. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for rifampin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5 mcg rifampin disk should be interpreted according to the following criteria for *Neisseria meningitidis*:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 20	(S) Susceptible
17-19	(I) Intermediate
≤ 16	(R) Resistant

Interpretation should be as stated above for results using dilution techniques.

As with standard dilution techniques, diffusion methods require the use of laboratory control microorganisms. The use of these microorganisms does not imply clinical efficacy (see INDICATIONS AND USAGE); they are used to control the technical aspects of the laboratory procedures. The 5 mcg rifampin disk should provide the following zone diameters in these quality control strains:

<u>Microorganism</u>		<u>Zone Diameter (mm)</u>
<i>S. aureus</i>	ATCC 25923	26 - 34
<i>E. coli</i>	ATCC 25922	8 - 10
<i>H. influenzae</i>	ATCC 49247	22 - 30

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

Following the initial phase, treatment should be continued with rifampin and isoniazid (eg, 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 establishment of the carrier state and the correct treatment. So 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

Rifampin is contraindicated in patients with a history of hypersensitivity to any of the rifamycins. (See WARNINGS.)

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 of necessity and then with caution and under strict medical supervision. In these 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 withdrawn.

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

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

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.**

PRECAUTIONS

General

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 reactions (leukopenia, thrombocytopenia, or acute hemolytic anemia), cutaneous, gastrointestinal, and hepatic reactions, shortness of breath, shock, anaphylaxis, and renal failure. Recent studies indicate that regimens using twice-weekly doses of rifampin 600 mg plus isoniazid 15 mg/kg are much better tolerated.

Intermittent therapy may be used if the patient cannot (or will not) self-administer drugs on a daily basis. Patients on intermittent therapy should be closely monitored for compliance and

cautioned against intentional or accidental interruption of prescribed therapy, because of the increased risk of serious adverse reactions.

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 infusion have been observed. If these occur, the infusion should be discontinued and restarted at another site.

Information for Patients

Patients should be counseled that antibacterial drugs including rifampin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When 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 (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by rifampin or other antibacterial drugs in the future.

The patient should be told that rifampin may produce a reddish coloration of the urine, sweat, sputum, and tears, and the patient should be forewarned of this. Soft contact lenses may be permanently stained.

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.

Patients should be instructed to notify their physicians promptly if they experience any of the following: fever, loss of appetite, malaise, nausea and vomiting, darkened urine, yellowish discoloration of the skin and eyes, 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

ENZYME INDUCTION: Rifampin is known to induce certain cytochrome P-450 enzymes. Administration of rifampin with drugs that undergo biotransformation through these metabolic pathways may accelerate elimination of coadministered drugs. To maintain optimum therapeutic blood levels, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping concomitantly administered rifampin.

Rifampin has been reported to accelerate the metabolism of the following drugs: anticonvulsants (eg, phenytoin), antiarrhythmics (eg, disopyramide, mexiletine, quinidine, tocainide), oral anticoagulants, antifungals (eg, fluconazole, itraconazole, ketoconazole), barbiturates, beta-blockers, calcium channel blockers (eg, diltiazem, nifedipine, verapamil), chloramphenicol, clarithromycin, corticosteroids, cyclosporine, cardiac glycoside preparations, clofibrate, oral or other systemic hormonal contraceptives, dapsone, diazepam, doxycycline, fluoroquinolones (eg, ciprofloxacin), haloperidol, oral hypoglycemic agents (sulfonylureas), levothyroxine, methadone, narcotic analgesics, nortriptyline, progestins, quinine, tacrolimus, theophylline tricyclic antidepressants (eg, amitriptyline, nortriptyline) and zidovudine. It may be necessary to adjust the dosages of these drugs if they are given concurrently with rifampin.

Patients using oral or other systemic hormonal contraceptives should be advised to change to nonhormonal methods of birth control during rifampin therapy.

Rifampin has been observed to increase the requirements for anticoagulant drugs of the coumarin type. In patients receiving anticoagulants and rifampin concurrently, it is recommended that the prothrombin time be performed daily or as frequently as necessary to establish and maintain the required dose of anticoagulant.

Diabetes may become more difficult to control.

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

Concurrent use of ketoconazole and rifampin has resulted in decreased serum concentrations 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 rifampin is given concomitantly with either halothane or isoniazid, the potential for hepatotoxicity is increased. The concomitant use of rifampin and halothane should be avoided. Patients receiving both rifampin and isoniazid should be monitored close for hepatotoxicity.

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.

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 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.

Therapeutic levels of rifampin have been shown to inhibit standard microbiological assays for serum folate and vitamin B₁₂. Thus, alternate assay methods should be considered. Transient abnormalities in liver function tests (eg, 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

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 2 to 10 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.

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. 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.

Pregnancy–Teratogenic Effects

Category C. Rifampin has been shown to be teratogenic in rodents given oral doses of rifampin 15 to 25 times the human dose. Although rifampin has been reported to cross the placental barrier and appear in cord blood, the effect of RIFADIN, alone or in combination with other antituberculosis drugs, on the human fetus is not known. Neonates of rifampin-treated mothers should be carefully observed for any evidence of adverse effects. Isolated cases of fetal malformations have been reported; however, there are no adequate and well-controlled studies in pregnant women. Rifampin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Rifampin in oral doses of 150 to 250 mg/kg produced teratogenic effects in mice and rats. Malformations were primarily cleft palate in the mouse and spina bifida in the rat. The incidence of these anomalies was dose-dependent. When rifampin was given to pregnant rabbits in doses up to 20 times the usual daily human dose, imperfect osteogenesis and embryotoxicity were reported.

Pregnancy–Non-Teratogenic Effects

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

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. Rarely, hepatitis or a shock-like syndrome with hepatic involvement and abnormal liver function tests has been reported.

Hematologic

Thrombocytopenia has occurred primarily with high dose intermittent therapy, but has also been noted after resumption of interrupted treatment. It rarely occurs during well supervised daily therapy. This effect is reversible if the drug is discontinued as soon as purpura occurs. Cerebral hemorrhage and fatalities have been reported when rifampin administration has been continued or resumed after the appearance of purpura.

Rare reports of disseminated intravascular coagulation have been observed.

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

Agranulocytosis has been reported very rarely.

Central Nervous System

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

Psychoses have been rarely reported.

Ocular

Visual disturbances have been observed.

Endocrine

Menstrual disturbances have been observed.

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

Renal

Elevations in BUN and serum uric acid have been reported. Rarely, hemolysis, hemoglobinuria, hematuria, interstitial nephritis, acute tubular necrosis, renal insufficiency, and acute renal failure have been noted. These are generally considered to be hypersensitivity reactions. They usually occur during intermittent therapy or when treatment is resumed following intentional or

accidental interruption of a daily dosage regimen, and are reversible when rifampin is discontinued and appropriate therapy instituted.

Dermatologic

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

Hypersensitivity Reactions

Occasionally, pruritus, urticaria, rash, pemphigoid reaction, erythema multiforme including Stevens-Johnson Syndrome, toxic epidermal necrolysis, vasculitis, eosinophilia, sore mouth, sore tongue, and conjunctivitis have been observed.

Anaphylaxis has been reported rarely.

Miscellaneous

Rare reports of myopathy and muscular weakness have also been observed.

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

OVERDOSAGE

Signs and Symptoms

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

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.

Acute Toxicity

The LD₅₀ of rifampin is approximately 885 mg/kg in the mouse, 1720 mg/kg in the rat, and 2120 mg/kg in the rabbit.

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

Treatment

Intensive support measures should be instituted and individual symptoms treated as they arise. Since nausea and vomiting are likely to be present, gastric lavage is probably preferable to induction of emesis. Following evacuation of the 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. Active diuresis (with measured intake and output) will help promote excretion of the drug. Hemodialysis may be of value in some patients.

DOSAGE AND ADMINISTRATION

Rifampin can be administered by the oral route or by IV infusion (see INDICATIONS AND USAGE). IV doses are the same as those for oral.

See CLINICAL PHARMACOLOGY for dosing information in patients with renal failure.

Tuberculosis

Adults: 10 mg/kg, in a single daily administration, not to exceed 600 mg/day, oral or IV

Pediatric Patients: 10-20 mg/kg, not to exceed 600 mg/day, oral or IV

It is recommended that oral rifampin be administered once daily, either 1 hour before or 2 hours after a meal with a full glass of water.

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

Following the initial phase, treatment should be continued with rifampin and isoniazid (eg, 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.

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 24 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 (D5W) are stable at room temperature for up to 4 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 24 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) diltiazem hydrochloride and rifampin (6 mg/mL in normal saline) during simulated Y-site administration.

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 (Syrup NF), Simple Syrup (Humco Laboratories), Syrpalta[®] 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 ($25 \pm 3^{\circ}\text{C}$) or in a refrigerator ($2-8^{\circ}\text{C}$) 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 30 (NDC 0068-0508-30)
Bottles of 60 (NDC 0068-0508-60)
Bottles of 100 (NDC 0068-0508-61)

Storage: Keep tightly closed. Store in a dry place. Avoid excessive heat.

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

Storage: Avoid excessive heat (temperatures above 40°C or 104°F). Protect from light.

References:

1. National Committee for Clinical Laboratory Standards, Antimycobacterial Susceptibility Testing. Proposed Standard NCCLS Document M24-P, Vol. 10, No. 10, NNCLS, Villanova, PA, 1990.
2. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically -- Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December 1993.
3. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests -- Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.
4. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing; Fifth Informational Supplement, NCCLS Document M100-S5, Vol. 14, No. 16, NCCLS, Villanova, PA, December 1994.

Rx only

Rifadin capsules are manufactured for:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

Rifadin IV (rifampin for injection USP) is manufactured by:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

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