CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 064150

FINAL PRINTED LABELING

NDC 0185-0799-42

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).
Store in a dry place.
Protect from excessive heat.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/95

Rifampin Capsules, USP

300 mg

CAUTION: Federal law prohibits dispensing without prescription.

240 Capsules

Eon Labs

Each capsule contains:
Rifampin, USP 300 mg

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0799-42 8

NDC 0185-0799-05

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).
Store in a dry place.
Protect from excessive heat.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/95

Rifampin Capsules, USP

300 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Capsules

Eon Labs

Each capsule contains:
Rifampin, USP 300 mg

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0799-05 3

NDC 0185-0799-10

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).
Store in a dry place.
Protect from excessive heat.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/95

Rifampin Capsules, USP

300 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 Capsules

Eon Labs

Each capsule contains:
Rifampin, USP 300 mg

This is a bulk package. Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0799-10 7

Exp. Date:

Lot No.:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).
Store in a dry place.
Protect from excessive heat.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/95

NDC 0185-0799-08

Rifampin Capsules, USP

300 mg

CAUTION: Federal law prohibits dispensing without prescription.

8 Capsules

Eon Labs

Each capsule contains:
Rifampin, USP 300 mg

Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0799-08 4

Exp. Date:

Lot No.:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).
Store in a dry place.
Protect from excessive heat.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/95

NDC 0185-0799-30

Rifampin Capsules, USP

300 mg

CAUTION: Federal law prohibits dispensing without prescription.

30 Capsules

Eon Labs

Each capsule contains:
Rifampin, USP 300 mg

Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0799-30 5

Exp. Date:

Lot No.:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).
Store in a dry place.
Protect from excessive heat.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/95

NDC 0185-0799-60

Rifampin Capsules, USP

300 mg

CAUTION: Federal law prohibits dispensing without prescription.

60 Capsules

Eon Labs

Each capsule contains:
Rifampin, USP 300 mg

Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0799-60 2

Exp. Date:

Lot No.:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).
Store in a dry place.
Protect from excessive heat.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Issued 3/95

NDC 0185-0799-01

Rifampin Capsules, USP

300 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Capsules

Each capsule contains:
Rifampin, USP 300 mg

Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP/NF.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N 3 0185-0799-01 5

RIFAMPIN
CAPSULES, USP

0799

RIFAMPIN
CAPSULES, USP

MAY 28 199

DESCRIPTION

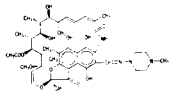
Rifampin is a semisynthetic antibiotic derivative of rifamycin SV. Rifampin is a red-brown crystalline powder very slightly soluble in water at neutral pH, freely soluble in chloroform, soluble in ethyl acetate and in methanol. Its molecular weight is 822.95 and its chemical formula is $C_{43}H_{58}N_4O_{12}$.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

3-[[(4-Methyl-1-piperazinyl)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-piperazinyl)-formimidoyl]-2,7(epoxypentadeca[1,11,13]trienimino)naphtho[2,1-*b*]furan-1,11(2H)-dione 21-acetate.

Its structural formula is:



Each capsule, for oral administration, contains 300 mg of rifampin. In addition, each capsule contains the following inactive ingredients: colloidal silicon dioxide, corn starch, D&C Yellow No. 10 Aluminum Lake, docusate sodium, FD&C Blue No. 1, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40, FD&C Red No. 40 Aluminum Lake, gelatin, magnesium stearate, microcrystalline cellulose, silicon dioxide, sodium benzoate, sodium lauryl sulfate, talc, titanium dioxide.

CLINICAL PHARMACOLOGY

Human Pharmacology:

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 µg/mL but may vary from 4 to 32 µg/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.

Pediatrics

In one study, pediatric patients 6 to 58 months old were given rifampin suspended in simple syrup or as dry powder mixed with applesauce at a dose of 10 mg/kg body weight. Peak serum concentrations of 10.7 ± 3.7 and 11.5 ± 5.1 µg/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, populations, at doses

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.

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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 position 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 µg/mL to determine drug resistance. After three weeks of incubation MIC_{99} values are calculated by comparing the quantity of organisms growing in the medium containing drug to the control cultures. Mycobacterial growth in the presence of drug, 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 µg/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*:

MIC (µg/mL)	Interpretation

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 µg/mL to determine drug resistance. After three weeks of incubation MIC_{99} values are calculated by comparing the quantity of organisms growing in the medium containing drug to the control cultures. Mycobacterial growth in the presence of drug, of at least 1% of the growth in the control culture, indicates resistance.

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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 is 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*:

MIC (µg/mL)	Interpretation
≤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:

Microorganism		MIC (µg/mL)
Staphylococcus aureus	ATCC 29213	0.008-0.06
Enterococcus faecalis	ATCC 29212	1-4
Escherichia coli	ATCC 25922	8-32
Pseudomonas aeruginosa	ATCC 27853	32-64
Haemophilus influenzae	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 µg 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 µg rifampin disk should be interpreted according to the following criteria for *Neisseria meningitidis*:

Zone Diameter (mm)	Interpretation
≥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; the ...

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008-0.06
1-4
8-32
32-64
0.25-1

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Zone Diameter (mm)	Interpretation
≥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 µg rifampin disk should provide the following zone diameters in these quality control strains:

Microorganism		Zone Diameter (mm)
S. aureus	ATCC 25923	26-34
E. coli	ATCC 25922	8-10
H. influenzae	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.

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 at 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.

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 patents taking rifampin with other hepatotoxic agents. Patents 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.

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

WARNINGS

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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 RIFAMPIN to short-term treatment of the asymptomatic carrier state. **RIFAMPIN is not to be used for the treatment of meningococcal disease.**

PRECAUTIONS

General

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.

Information for Patients

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

A complete blood count (CBC) and liver function tests 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 rifampin dosing.

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, 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, tacrolimus, theophylline 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.

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 enalaprilat. Dosage adjustments should be made if indicated by the patient's clinical condition.

Other Interactions: 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

Therapeutic levels of rifampin have been shown to inhibit standard microbiological assays for serum folate and vitamin B_{12}. 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 chromotid 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 RIFAMPIN, 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

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[illegible]
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 chromotid 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.

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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.

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.

Transient leukopenia, hemolytic anemia, and decreased hemoglobin have been observed.

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.

Rare reports of myopathy have also been observed.

Ocular

Visual disturbances have been observed.

Endocrine

Menstrual disturbances have been observed.

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

Renal

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

Dermatologic

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

Hypersensitivity Reactions

Occasionally, pruritus, urticaria, rash, pemphigoid reaction, erythema multi-

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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

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, and increasing lethargy will probably occur within a short time after ingestion; 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.

Liver enlargement, possibly with tenderness, may 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.

Acute Toxicity

The LD_{50} of rifampin is approximately 885 mg/kg in the mouse, 1720 mg/kg in the rat, and 2120 mg/kg in the rabbit.

Nonfatal overdoses with as high as 12 g of rifampin have been reported. In one patient who swallowed 12 g of rifampin, vomiting occurred four times within 1 hour of ingestion. Gastric lavage with 20 liters of water was initiated 5 hours after ingestion. Twelve hours after ingestion of rifampin, a plasma concentration of 400 µg of rifampin/mL was measured by microbiological assay. The plasma concentration fell to 64 µg/mL on the following day, and to 0.1 µg/mL on the third day. Urinary rifampin concentration was 313 g/mL approximately 30 hours after ingestion of the drug, 625 µg/mL after 36 hours, and 78 µg/mL after 40 hours. By the fourth day following the dose, only 0.1 µg/mL rifampin was present in the urine. There was biochemical evidence of mild impairment of liver function. Liver function tests had returned to normal within 5 days, and the patient's recovery was described as uneventful.

One case of fatal overdose is known: a 26-year-old man died after self-administering 60 g of rifampin.

Treatment

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. In patients with previously adequate hepatic function, reversal of liver enlargement and of impaired hepatic excretory function probably will be noted within 72 hours, with a rapid return toward normal thereafter.

DOSAGE AND ADMINISTRATION

Rifampin can be administered by the oral route (see INDICATIONS AND USAGE).

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

Tuberculosis

Adults: 600 mg in a single daily administration.

Pediatric Patients: 10-20 mg/kg not to exceed 600 mg/day.

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

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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.

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:

Rifampin 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 contents of four rifampin 300 mg capsules or eight rifampin 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 rifampin powder blend to a 4-ounce amber glass 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

Rifampin Capsules USP 300 mg are supplied as red capsules, imprinted E 799 and are available in bottles of: 30, 60, 100 and 500.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F). **Store in a dry place.** Avoid excessive heat.

Caution: Federal law prohibits dispensing without prescription.

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