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 formate, sodium carbonate, 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 \( C_{31}H_{47}O_{26}N_{12} \). 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-2-(N-[4-(4-Methyl-1-piperazinyl)formimidoyl][2,7-(epoxypentadeca[1,11,13]triienimino)naphtho][2,1-f]-furain-1,11(2H)-dione-21-acetate. Its structural formula is:

CLINICAL PHARMACOLOGY

Oral Administration
Rifampin is rapidly 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. The half-life of rifampin at a dose of 720 mg daily has not been established in patients with renal failure. Following a single 900 mg oral dose of rifampin in patients with varying degrees of renal insufficiency, the mean half-life increased from 3.6 hours in healthy adults to 5.0, 7.3, and 11.0 hours in patients with glomerular filtration rates of 30 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 male volunteers (n=12), mean peak plasma concentrations were 9.8 ± 3.0 and 17.5 ± 5.0 mcg/mL, respectively. Total body clearances after the 300 and 600 mg IV doses were 0.28 ± 0.08 and 0.44 ± 0.08 L/hr/kg, respectively. Volumes of distribution at steady state were 0.06 ± 0.14 and 0.04 ± 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).

<table>
<thead>
<tr>
<th>Rifampin Dosage IV</th>
<th>30 min</th>
<th>1 hr</th>
<th>2 hr</th>
<th>4 hr</th>
<th>8 hr</th>
<th>12 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg</td>
<td>8.9±2.9</td>
<td>4.9±1.3</td>
<td>4.0≤1.3</td>
<td>2.5≤1.0</td>
<td>1.1±0.6</td>
<td>≤0.4</td>
</tr>
<tr>
<td>600 mg</td>
<td>17.4±5.1</td>
<td>11.7±2.8</td>
<td>9.4±2.3</td>
<td>6.4±1.7</td>
<td>3.5±1.4</td>
<td>1.2±0.6</td>
</tr>
</tbody>
</table>

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 to 1.26 ± 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 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 t1/2 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
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.

Drug 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 clinical failures.

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 INDIICATIONS 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)
  - Straphylococcus epidermidis

- Anaerobic Gram-Negative Microorganisms:
  - Haemophilus influenzae
  - "Other" Microorganisms:
  - Mycobacterium leprae

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

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

In vitro testing for Mycobacterium tuberculosis isolates:
Two standardized in vitro susceptibility methods are available for testing rifampin against M. tuberculosis organisms. The agar proportion method (CDC or CLSIM 2004) utilizes Middlebrook 7H110 medium impregnated with rifampin at a final concentration of 1.0 mcg/mL to determine drug resistance. After three weeks of incubation MIC 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.
Rifampin is indicated in the treatment of all forms of tuberculosis. If a patient is not responding to therapy, the drug regimen should be modified. Resistance testing should be repeated throughout therapy to monitor the response to treatment. Since resistance can 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. 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 pharmakokinetic 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:

**In vitro testing for Neisseria meningitidis isolates:**

**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 has been recommended for use with disks to test the susceptibility of microorganisms to rifampin. This method 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:

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 20</td>
<td>(S) Susceptible</td>
</tr>
<tr>
<td>17–19</td>
<td>(I) Intermediate</td>
</tr>
<tr>
<td>≤ 16</td>
<td>(R) Resistant</td>
</tr>
</tbody>
</table>

Interpretation should be as stated above for results using diffusion 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:

**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 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 5%, one additional drug is recommended for the initial treatment regimen.

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.)

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:

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>ATCC 29213</td>
</tr>
<tr>
<td>E. coli</td>
<td>ATCC 29222</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>ATCC 27853</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>ATCC 49247</td>
</tr>
</tbody>
</table>

**Microorganism**

**MIC (mcg/mL)**

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>0.008 – 0.06</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>1 – 4</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>8 – 32</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>32 – 64</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>0.25 – 1</td>
</tr>
</tbody>
</table>

**Interpretation**

**S. aureus**

ATCC 29223: 28 – 34

**E. coli**

ATCC 29222: 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.

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 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

Quantitative methods that are used to determine minimum inhibitory concentrations may be appropriate to guide therapy in some situations. 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:

<table>
<thead>
<tr>
<th>Organism</th>
<th>MIC (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>0.008 – 0.06</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>1 – 4</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>8 – 32</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>32 – 64</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>0.25 – 1</td>
</tr>
</tbody>
</table>

**Interpretation**

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 20</td>
<td>(S) Susceptible</td>
</tr>
<tr>
<td>17–19</td>
<td>(I) Intermediate</td>
</tr>
<tr>
<td>≤ 16</td>
<td>(R) Resistant</td>
</tr>
</tbody>
</table>

In vitro testing for Neisseria meningitidis isolates:

**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 has been recommended for use with disks to test the susceptibility of microorganisms to rifampin. This method 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:

<table>
<thead>
<tr>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 20</td>
<td>(S) Susceptible</td>
</tr>
<tr>
<td>17–19</td>
<td>(I) Intermediate</td>
</tr>
<tr>
<td>≤ 16</td>
<td>(R) Resistant</td>
</tr>
</tbody>
</table>

Interpretation should be as stated above for results using diffusion 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:

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Zone Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>ATCC 25923: 28 – 34</td>
</tr>
<tr>
<td>E. coli</td>
<td>ATCC 25922: 8 – 10</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>ATCC 49247: 22 – 30</td>
</tr>
</tbody>
</table>

**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.

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 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
For intravenous infusion only. Must not be administered by intramuscular or subcutaneous route. Avoid extravasation during injection: local irritation and inflammation due to extravasational 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 contraceptive methods 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 physician immediately if they experience any of the following: early manifestations of hypersensitivity, such as severe rash, fever, or swollen lymph nodes. Patients should be instructed to notify their physicians promptly if they experience any of the following: 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 (e.g., liver disease or renal dysfunction) is 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**

Healthy subjects who received rifampin 600 mg once daily concomitantly with saquinavir 1000 mg tid and ritonavir 400 mg bid for 14 days developed increased concentrations of saquinavir and ritonavir. These antiviral drugs must not be coadministered with rifampin. (See CONTRAINDICATIONS.)

**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 substantially decrease the plasma concentrations of the following antiviral drugs: atazanavir, darunavir, fosamprenavir, saquinavir, and tipranavir.

**Hematologic**

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.

**Gastrointestinal**

Hepatobiliary abnormalities in liver function tests (e.g., elevations 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 periodically in patients taking rifampin.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

A few cases of accelerated growth of lung carcinoma have been reported in men, but a causal relationship with the drug has not been established. Hepatomas were increased in female (C3H/DP) mice dosed for 80 weeks with rifampin followed by an observation period of 46 weeks, at a daily dose of up to 120 mg/kg (equivalent to 0.1 to 0.2 times the maximum dosage used clinically, based on body surface area comparisons). There was no evidence of tumorigenicity in male C3H/DP mice or in similar studies in BALB/c mice, or in two year studies in Wistar rats.

There was no evidence of mutagenicity in both prokaryotic (Salmonella typhimurium and Escherichia coli) and eukaryotic (Saccharomyces cerevisiae) bacteria, Drosophila melanogaster, or ICR/Ha Swiss mice. An increase in chromatid breaks was noted when whole blood cell cultures were treated with rifampin. Increased frequency of chromosomal aberrations was observed in vitro in lymphocytes obtained from patients treated with combinations of rifampin, isoniazid, and pyrazinamide and combinations of streptomycin, rifampin, isoniazid, and pyrazinamide.

**Nursing Mothers**

Pregnancy–Non-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 fetuses of pregnant mice treated at oral doses of 50 to 200 mg/kg (about 0.2 to 0.8 times the maximum recommended human dose based on body surface area comparisons). Imperfect osteogenesis and embryotoxicity were also reported in pregnant rabbits given rifampin at oral doses up to 200 mg/kg/day (about 3 times the maximum recommended 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. Rifampin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy–Teratogenic Effects

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.

**Adverse Reactions**

Skin: Rash, maculopapular rash, pruritus, urticaria, exfoliative dermatitis, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, erythrodermia, bullous eruption, erythema nodosum, pustular rash, drug reaction with eosinophilia (DRESS), Stevens-Johnson syndrome, and toxic epidermal necrolysis have been observed. Rare reports of myopathy have also been observed.

**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 (e.g., Abuscreen OnLine opiates assay; Roche Diagnostic Systems). Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish rifampin from opiates.

Therapeutic levels of rifampin have been shown to inhibit standard microbiological assays for serum folate and vitamin 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 periodically in patients taking rifampin.

**Hematologic**

Transient abnormalities in liver function tests (e.g., elevations in serum bilirubin, alkaline phosphatase, serum transaminases) have been observed. Rare, hepatitis or a shock-like syndrome with hepatic involvement and abnormal liver function tests has been reported. Hemolytic Anemia

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 therapy 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**

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

Psychoses have been rarely reported. Rare reports of myopathy have also been observed.
Ocular
Visual disturbances have been observed.

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

Renal
Elevations in BUN and serum uric acid have been reported. Rarely, hemolytic, 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, pempigoid reaction, erythema multiforme including Stevens-Johnson Syndrome, toxic epidermal necrolysis, Drug Reaction with Eosinophilia and Systemic Symptoms syndrome (see WARNINGS), vasculitis, eosinophilia, sore mouth, sore tongue, and conjunctivitis have been observed. Anaphylaxis has been reported rarely.

Miscellaneous
Edema of the face and extremities has been reported. Other reactions which have occurred with intermittent dosage regimens include "flu syndrome" (such as episodes of fever, chills, headache, dizziness, and bone pain), shortness of breath, wheezing, decrease in blood pressure and shock. The "flu syndrome" may also appear if rifampin is taken irreguiarly 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. Liver enlargement, possibly with tenderness, can develop within a few hours after severe overdosage; bilirubin levels may increase and jaundice may develop rapidly. Hepatic involvement may be more marked in patients with prior impairment of hepatic function. Other physical findings remain essentially normal. A direct effect upon the hematopoietic system, electrolyte levels, or acid-base balance is unlikely.
Facial or periorbital edema has also been reported in pediatric patients. Hypotension, sinus tachycardia, ventricular arrhythmias, seizures and cardiac arrest were reported in some fatal cases.

Acute Toxicity
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 supportive measures should be instituted and individual symptoms treated as they arise. The airway should be secured and adequate respiratory exchange established. Since nausea and vomiting are likely to be present, gastric lavage within the first 2 to 3 hours after ingestion of rifampin by emesis is recommended. Followings evacuation of the gastric contents, the instillation of activated charcoal slurry into the stomach may help absorb any remaining drug from the gastrointestinal tract. Anlhetic medication may be required to control severe nausea and vomiting.
Active diuresis (with measured intake and output) will help promote excretion of the drug. For severe cases, extracorporeal hemodialysis may be required. If this is not available, peritoneal dialysis can be used along with forced diuresis.

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 may be added to 100 mL of infusion medium and infused in simulated Y-site administration.

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), SpyPalta® 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 60 (NDC 0068-0508-30)
Bottles of 100 (NDC 0068-0508-61)
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 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 SÁNGOFI COMPANY

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

Revised October 2016
©2016 sanofi-aventis U.S. LLC
RIF-FSP-L-SL-OCT16

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.