RIFAMPIN (Veterinary—Systemic)

Some commonly used brand names for human-labeled products are: Rifadin; Rifadin IV; Rimactane; and Refact.

Category: Antibacterial (systemic).

Indications

Note: Rifampin is not specifically approved for veterinary use. In other USP information monographs the ELUS and CAN designations refer to uses that are not included in U.S. and Canadian product labeling; however, in this monograph they reflect the lack of veterinary products and, therefore, product labeling.

General considerations

Rifampin is a broad-spectrum antibiotic, with activity against many gram-positive and some gram-negative aerobic bacteria as well as facultative anaerobic organisms. However, for clinical purposes, rifampin generally should not be considered broad-spectrum until proven so in each case. Most gram-negative bacteria should be considered resistant or to have unpredictable susceptibilities until susceptibility data are available. Because many infections involve more than one species of bacterium and because resistance can develop quickly, rifampin is most often administered in combination with other antimicrobials.

Rifampin is considered especially active in the treatment of staphylococcal infections and in the eradication of pathogens located in difficult target areas, such as inside phagocytic cells. The ability of rifampin to reach intracellular bacteria can make it difficult to predict in vivo therapy results based on in vitro sensitivity tests.

Rifampin has been shown to have in vitro activity against equine Corynebacterium pseudotuberculosis, Rhodococcus equi, Staphylococcus species, Streptococcus equi, S. equisimilis, and S. zoogenes isolates. Susceptibility has been variable for the equine gram-negative nonfermentive bacterium. It has shown moderate activity against Actinobacillus suis, A. equi, Bordetella bronchiseptica, and Pasteurella species isolates. Equine isolates of Pseudomonas aeruginosa, Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae, Proteus species, and Salmonella species were found to be resistant.

Strains of the porcine pathogen Actinobacillus pleuropneumoniae, isolated in Spain, were found to be susceptible to rifampin in vitro at a concentration of 1 mcg/mL or less. Rifampin also had activity against Pasteurella multocida species isolated from pigs with pneumonia in Spain.

Some strains of Mycobacterium paratuberculosis were found to be sensitive to rifampin in vitro tests.

Anaerobes found to be susceptible in vitro include 132 strains of Bacteroides species and 25 strains of Fusobacterium species isolated from goats in Spain; with blood concentrations of 2 mcg/mL, only 18% of strains were resistant. Although in vitro tests showed rifampin to be active against Clostridium perfringens type A isolates, when higher concentrations of pathogens per milliliter were tested, the antimicrobial was not very effective and in vivo efficacy against induced infections in mice was only weakly significant.

Resistance to rifampin can develop quickly; therefore, it is most often used in combination with other antimicrobials. Resistant mutants may be concentration-sensitive and contain RNA polymerases with one of a variety of sensitivities to rifampin.

Resistance may occur as a single-step mutation of the DNA-dependent RNA polymerase; therefore, initial susceptibility can rapidly diminish as the populations of resistant cells soon outnumber susceptible cells. This effect is diminished when combination antibiotic treatment is administered. One case of the development of resistant Rhodococcus equi in a foal treated with erythromycin and rifampin has been reported. Cross-resistance to other antibiotics or transfer of resistance to other local microorganisms has not been reported.

Accepted

Pneumonia, Rhodococcus equi (treatment adjunct) or Extrapulmonary infection, Rhodococcus equi (treatment adjunct)—Foals: Rifampin is used in combination with erythromycin in the treatment of pneumonia caused by Rhodococcus (Corynebacterium) equi infection in foals. Although the lung appears to be most vulnerable to Rhodococcus equi infection, in some cases susceptible foals have been found to have abdominal or septic lesions, diskospondylitis, gastrointestinal infections, ostoemyelitis, or septicemia. In many, but not all of these cases, the foal has an accompanying pneumonia.

R. equi are susceptible in vitro to erythromycin alone, and erythromycin alone has been effective in the treatment of this infection. However, no studies have been performed to compare the efficacy of erythromycin alone with a combination of erythromycin and rifampin in foals. The in vitro evidence of synergistic activity for the combination of erythromycin and rifampin against R. equi and the volume of case reports supporting the efficacy of the combination make treatment with a combination of erythromycin and rifampin more commonly recommended for this indication than erythromycin alone.

Potentially effective

Infections, bacterial (treatment)—Although the safety and efficacy have not been established, rifampin is used in combination with other antimicrobials in the treatment of susceptible bacterial infections, and in particular, staphylococcal infections in animals. Rifampin is particularly suited for the treatment of organisms that are resistant to other therapies by nature of their intracellular location. Because the pharmacokinetics of rifampin have been well-studied in horses, minimal side effects have been reported in foals. The treatment of these infections in horses may be more well-defined than for other species. The use of rifampin in other animals could be based on available pharmacokinetic data for calves, sheep, and dogs. The safety and efficacy have not been established.

There are no controlled studies in dogs.

Brucellosis (treatment)—Dogs: Although the safety and efficacy have not been established, rifampin in combination with doxycycline has been recommended in the treatment of brucellosis in dogs. This recommendation is based on demonstrated efficacy in the treatment of human brucellosis and evidence of possible canine pathogen susceptibility to rifampin.

Brucellosis (treatment)—Cattle, goats, and sheep: For use in animals not to be used in the production of human food—Although the safety and efficacy have not been established, rifampin has been administered in conjunction with isoniazid in the alleviation of signs associated with paratuberculosis (Mycobacterium paratuberculosis infection or Johne’s disease). The addition of an aminoglycoside to the regimen has also been used in the initial weeks of severe infection, and on case reports of clinical improvement for extended periods of time. However, internal lesions and fecal shedding of the organism are rarely controlled. It should be noted that semen from bulls with paratuberculosis have been found to contain M.

© 2007 The United States Pharmacopeial Convention
paratuberculosis even after freezing and processing. Placental infection of a fetus can occur in infected cows.\[5-23\] It is not known if rifampin and isoniazid therapy can prevent transmission in semen or transplacentally. The cost of rifampin therapy, as well as the inability to completely clear infection and prevent spread of disease, limits treatment to valuable quarantined animals.\[5-23; 44\]

### Potomac horse fever (treatment)\[9-11]\n
**Horses:** Although the efficacy is not established, rifampin is used in combination with erythromycin in the treatment of Potomac horse fever (equine choriald colitis).\[5-20\] It is as effective as oxytetracycline in the resolution of clinical signs, with the exception that rifampin and erythromycin will not reduce fever as quickly as oxytetracycline, taking up to 12 hours longer to return the body temperature to normal.\[5-56\] Rifampin and erythromycin have the advantage of being available in oral dosage forms.

### Unaccepted\[5-15; 56\]

**Mycobacterial infections (treatment)**\[6-11\]: Current therapeutic regimens for mycobacterial infections cannot guarantee that an animal is no longer contagious during treatment. Treatment of *Mycobacterium tuberculosis*, *Mycobacterium bovis*, and other mycobacterial species transmissible to human beings is nearly always considered inappropriate.\[5-45; 47\] The treatment of tuberculosis in cattle is not permitted in Canada or the U.S.\[5-64\]

The treatment of mycobacterial infections that do not cause human tuberculosis, such as atypical mycobacterial infections in cats, may be acceptable\[5-45; 48\] although there is insufficient evidence of efficacy at this time.

### Regulatory Considerations

**U.S. and Canada—**Rifampin is not labeled in the United States or Canada for use in animals, including food-producing animals. There are no established withdrawal times. The treatment of tuberculosis in cattle is not permitted in Canada or the U.S.\[5-64\]

### Chemistry

**Source:** Semisynthetic derivative of rifamycin B.\[5-2; 4\] A natural fermentation product of *Nocardia* (*Streptomyces*) *mediterranea*.\[5-4, 6\]

**Chemical group:** Macro cyclic antibiotic.\[5-13\]

**Chemical name:** Rifamycin, 3-[[[(4-methyl-1-piperazinyl)iminomethyl]amino]methyl]-\[5-22\]

**Molecular formula:** C_{43}H_{58}N_{4}O_{12}.\[5-1\]

**Molecular weight:** 822.94.\[5-1\]

**Description:** Rifampin USP—Red-brown, crystalline powder.\[5-3\]

**pKa:** 7.9.\[5-22\]

**Solubility:** Rifampin USP—Very slightly soluble in water; freely soluble in chloroform; soluble in ethyl acetate and in methanol.\[5-22\]

### Pharmacology/Pharmacokinetics

**Mechanism of action/Effect:** Rifampin inhibits DNA-dependent RNA polymerase; however, at therapeutic doses, it inhibits the enzyme in bacteria, while not affecting mammalian polymerase.\[5-2; 4\] Rifampin is bactericidal and is active against extracellular as well as intracellular bacteria.\[5-2; 8; 49\] including intraleukocytic organisms.\[5-20\] Rifampin can enter neutrophils and macrophages to kill intracellular bacteria,\[5-4; 10\] while not interfering with phagocytosis.\[5-29\]

Rifampin appears to penetrate the outer membrane of gram-positive bacteria more easily than that of gram-negative bacteria.\[5-4\] This is reflected in the significantly lower minimum inhibitory concentrations (MIC) required for gram-positive bacteria (0.01 mcg per mL of serum) compared with gram-negative bacteria (8 to 32 mcg per mL).\[5-4\]

### Absorption:

Rifampin is rapidly absorbed after oral administration to calves, dogs, horses, and human beings.\[5-13; 41; 19\] although bioavailability is not high in horses and sheep. Administration with food can prolong the time to peak serum concentration in adult horses and people.\[5-4; 20\] Adult sheep appear to have prolonged absorption, possibly because of prolonged movement through the rumen.\[5-20\]

### Bioavailability—

**Oral:**

**Horses—**

48.8%, with a single dose of 10 mg per kg of body weight (mg/kg).\[5-4\]

39.5%, with a single dose of 10 mg/kg, administered in the feed.\[5-13\]

Note: An unpublished study of horses receiving a dose of 5 mg/kg found a bioavailability of 68% when rifampin was administered 1 hour before feeding and 26% when it was administered 1 hour after feeding.\[5-13\] Because rifampin is most often administered with feed, recommended dosages compensate for the decreased absorption.

**Sheep—**

36.6 ± 3.2%, with a dose of 10 mg/kg, as an oral drench.\[5-19\]

3 to 3.2%, with a dose of 20 mg/kg, in a gel capsule.\[5-21\]

14 to 122%, with a dose of 50 mg/kg, in a gel capsule.\[5-21\]

Note: The study performed using gel capsules of rifampin in sheep found that absorption was incomplete and still continuing by the end of the study, producing extremely variable results.\[5-21\] Absorption was also relatively low and variable with the oral drench but not to the same extent as with gel capsules; the medication may have been administered directly into the abomasum and would therefore have been rapidly and consistently absorbed.\[5-21\]

### Distribution:

Rifampin is highly lipid-soluble and is widely distributed in tissues.\[5-4; 6\] Antimicrobial concentrations are approached in all tissue compartments throughout the body, including milk.\[5-22\] Bone.\[5-64\] cerebrospinal fluid.\[5-18\] exudates, ascitic fluid, and soft tissues.\[5-6\] Rifampin crosses the blood-brain barrier and, in rabbits, the cerebrospinal fluid to plasma concentration ratio ranged from 0.52 to 1.17, from 30 minutes to 12 hours after an oral dose of 10 mg/kg.\[5-16; 18\] Rifampin can penetrate phagocytic cells to kill susceptible intracellular bacteria.\[5-4; 7; 29\] In many species, as has been documented in dogs and human beings, feaces, saliva, sweat, tears, and urine may be discolored red-orange by rifampin and its metabolites.\[5-4\]

### Volume of distribution—

**Horses:** Area—0.93 ± 0.29 liter per kg (L/kg).\[5-7; 25; 26\] 0.63 ± 0.06 L/kg.\[5-13\]

Steady state—0.76 L/kg.\[5-4\]

**Sheep:** Steady state—0.45 ± 0.06 L/kg.\[5-21\]

### Protein binding:

**Horses—**High (78%).\[5-4\] with serum concentrations of 2 to 20 micrograms per milliliter (mcg/mL).\[5-4\]

**Human beings—**High (90%).\[5-4\]

**Sheep—**High (84%).\[5-22\]

### Biotransformation:

The biotransformation and elimination of rifampin in animals is not well defined. Induction of hepatic enzymes occurs in response to administration of rifampin in many species,\[5-13; 17; 22; 26\] but major
metabolites of the parent drug in most animals have not yet been traced.\cite{R-6, R-21} In human studies, it was found that the primary metabolite of rifamipin is 25-desacetylrifampin, which is bioactive.\cite{R-4} Human desacetylrifampin is more profusely secreted in the bile compared with rifampin, but is less concentrated in the serum than the parent drug.\cite{R-6} And while rifampin undergoes extensive human enterohepatic recycling, desacetylrifampin is poorly absorbed and therefore is not recycled.\cite{R-6}

**Horses**—Desacetylrifampin was not detected in serum samples after an intravenous dose of 10 mg/kg or oral doses of 10 mg/kg every 12 hours for seven doses.\cite{R-4} The metabolite was measured in urine, but the parent compound was much more predominant;\cite{R-6} however, only 6.82% of the total dose was recovered in the urine as either rifampin or desacetylrifampin.\cite{R-6}

**Rats**—Desacetylrifampin is formed in extremely low quantities in rats.\cite{R-25}

**Sheep**—Desacetylrifampin was not found in serum samples from sheep administered either intravenous or oral rifampin.\cite{R-21} Rifampin and metabolites have not been measured in sheep urine.

Rifampin can induce hepatic enzymes, including increasing its own hepatic biotransformation with multiple doses.\cite{R-17, R-26} Induction has been shown to occur in many species, including dogs,\cite{R-27} pigs,\cite{R-30} and rabbits.\cite{R-28, R-29} The dose needed to induce an increase in hepatic enzymes varies among species. Rats administered 50 mg/kg intraperitoneally every 12 hours for 6 days did not show induction of liver microsomal enzyme activity against substances tested,\cite{R-26} but mice administered the same dose showed significant induction of the hepatic mixed-function oxidase system and enzymatic activity.\cite{R-26} In horses, enzyme induction has generally not been seen with less than 5 days of therapy, but once there is an increase in hepatic enzyme activity, the increase may last for more than 2 weeks after discontinuation of treatment.\cite{R-27} However; several factors may modify the therapeutic levels of rifampin, such as the variability in its absorption in horses when given alone, and the possible change in pharmacokinetics due to interactions with other medications that often are administered with rifampin; data are insufficient for determining whether the increased elimination of rifampin due to hepatic enzyme induction during prolonged dosing may be corrected for by a dose modification.

**Half-life:**

**Absorption**—

Intramuscular administration: **Horses**—6.7 ± 1.5 hours, with a dose of 10 mg/kg.\cite{R-13}

Oral, with food: **Horses**—

4.2 ± 1.2 hours, with a dose of 10 mg/kg.\cite{R-13}

2.6 ± 1.3 hours, with a dose of 25 mg/kg.\cite{R-13}

Distribution—Intravenous: **Horses**—13.8 ± 5.2 minutes, with a dose of 10 mg/kg.\cite{R-13}

Elimination—

Intravenous:

**Horses**—8.1 hours;\cite{R-16} 7.3 hours;\cite{R-7} 6 hours.\cite{R-13}

**Sheep**—2.9 hours;\cite{R-19} 4.56 hours.\cite{R-21}

**Sheep**, lactating—3.3 hours.\cite{R-22}

Intramuscular (terminal elimination)—

**Horses**—7.3 hours, with a dose of 10 mg/kg.\cite{R-13}

**Sheep**—11 hours, with a dose of 20 mg/kg.\cite{R-22}

Oral (terminal elimination)—

Single dose:

**Dogs**—8 hours, with a dose of 10 mg/kg.\cite{R-4, R-48}

**Foals**—

1 week of age: 25.4 ± 1.2 hours, with a dose of 10 mg/kg.\cite{R-14}

10 weeks of age: 7.9 ± 1.5 hours, with a dose of 10 mg/kg.\cite{R-14}

**Horses**—13.3 hours, with a dose of 10 mg/kg.\cite{R-64}

**Sheep**—6.42 hours, with a dose of 20 mg/kg.\cite{R-81}

Multiple doses: **Horses**—299 hours, after the seventh dose of 10 mg/kg, administered every 12 hours.\cite{R-6}

Note: Multiple doses result in lower peak serum concentrations and a decreased half-life, because of autoinduction of hepatic enzymes.\cite{R-4}

**Concentrations:**

Peak serum concentration—Autoinduction of hepatic enzymes can cause multiple doses of rifampin to result in lower peak serum concentrations than expected, if based on single dose measurements.\cite{R-4, R-19}

**Intramuscular:**

**Horses**—4 ± 0.3 mcg/mL at 4.2 ± 0.2 hours after a dose of 10 mg/kg.\cite{R-33}

**Sheep**—Approximately 8 mcg/mL (from graph) at 3 hours after a dose of 20 mg/kg.\cite{R-22}

Oral:

**Calves**—2 to 3 weeks of age—11.7 to 24.6 mcg/mL at 4 to 8 hours after a dose of 10 mg/kg.\cite{R-4, R-48}

**Dogs**—40 mcg/mL at 2 to 4 hours after a dose of 10 mg/kg.\cite{R-4, R-48}

**Foals**—6 to 8 weeks of age—6.7 mcg/mL at 4 hours after a dose of 10 mg/kg.\cite{R-64}

**Horses**—

3.9 mcg/mL at 3 hours;\cite{R-4} 4.5 ± 1.1 mcg/mL at 1.6 ± 0.5 hours after a dose of 10 mg/kg.\cite{R-14}

2.9 ± 0.4 mcg/mL at 3.7 ± 1.2 hours;\cite{R-19} 3.3 ± 2.9 mcg/mL at 3.5 ± 1.7 hours after a dose of 10 mg/kg, administered with food.\cite{R-14}

13.3 ± 2.7 mcg/mL at 2.5 hours after intragastric administration of oral suspension at a dose of 20 mg/kg.\cite{R-7}

9.8 ± 1.9 mcg/mL at 3.5 hours after a dose of 25 mg/kg, administered with food.\cite{R-13}

**Sheep**—

0.6 to 2.4 mcg/mL at 4 to 8 hours, with a dose of 10 mg/kg.\cite{R-4, R-48}

3.27 ± 1.43 mcg/mL at 8 to 24 hours, with a dose of 20 mg/kg.\cite{R-22}

Other concentrations—

**Cerebrospinal fluid:** **Rabbits**—1.3 to 1.6 mcg/mL from 30 minutes to 12 hours after an oral dose of 10 mg/kg.\cite{R-18}

**Serum:**

**Dogs**—9 to 10 mcg/mL, 24 hours after an oral dose of 10 mg/kg.\cite{R-65}

**Horses**—

6.86 ± 1.69 mcg/mL, 12 hours after an intragastric dose of 20 mg/kg of oral suspension.\cite{R-7}

3.83 ± 0.87 mcg/mL, 24 hours after an intragastric dose of 20 mg/kg of oral suspension.\cite{R-7}

**Rabbits**—

Ranged from 1.8 to 2.5 mcg/mL from 30 minutes to 12 hours after an oral dose of 10 mg/kg.\cite{R-18}

**Sheep**—0.97 ± 0.61 mcg/mL, 24 hours after an oral dose of 20 mg/kg in a gelatin capsule.\cite{R-21}

**Duration of action:** The National Committee for Clinical Laboratory Standards (NCCLS) in the United States lists minimum inhibitory concentration (MIC) breakpoints for animal isolates and rifampin as ≤ 1 mcg/mL for susceptible organisms and ≥ 4 mcg/mL for resistant organisms.\cite{R-8}

**Dogs:** Serum concentration was 9 to 10 mcg/mL 24 hours after a single oral dose of 10 mg/kg.\cite{R-45}

**Horses:** Serum concentrations greater than 2 mcg/mL were reached 45 minutes after intragastric rifampin administration of 20 mg/kg and concentrations were maintained at greater than 3 mcg/mL for at least 24 hours.
Elimination: Horses: Only 6.82% of the intravenous dose of 10 mg/kg was recovered in the urine as rifampin or desacetylrifampin, an active metabolite. It is not known if the rifampin that is not recovered is predominately sequestered in the tissue or perhaps excreted in bile primarily as desacetylrifampin, a more polar and more easily bile-excreted compound.

Total clearance—

Horses: 1.14 mL/min/kg; Sheep: 1.34 mL/min/kg.

Precautions to Consider

Species sensitivity

Dogs: There is very little information about the effects of rifampin in small animals; however, there is anecdotal information warning that up to 20% or more of dogs receiving 5 to 10 mg per kg of body weight (mg/kg) a day will develop increases in hepatic enzymes that may lead to clinical hepatitis. Because one study found peak serum concentrations in dogs that were four times that of horses after a standard dose of 10 mg/kg, it has been suggested that the incidence of side effects in dogs may be due to overdosage. Some clinicians have noted lethargy, bilirubinemia, and bilirubinuria in dogs administered rifampin, but there is no information on incidence of adverse effects, dosage administered, pretreatment liver evaluation, or other factors.

Tumorigenicity

Studies in female mice of a strain known to be particularly susceptible to the spontaneous development of hepatomas have shown that rifampin, given in doses of 2 to 10 times the maximum human dose (20 mg per kg of body weight, up to 600 mg every 12 hours) for 1 year, caused a significant increase in the development of hepatomas. However, studies in male mice of the same strain, in other strains of male or female mice, and in rats have not shown that rifampin is tumorigenic.

Pregnancy/Reproduction

Mice and rats: Oral doses of 150 to 250 mg/kg during pregnancy produced dose-dependent teratogenic effects in offspring including cleft palate in the mouse and spina bifida in the rat.

Human information: Rifampin has caused postnatal hemorrhage in the rat. Treatment with vitamin K may be indicated.

Lactation

Sheep: Rifampin is well-distributed into milk, with a milk to serum concentration ratio of 0.9 to 1.28 in sheep given an intramuscular dose of 10 mg/kg.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (« = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Drugs metabolized by hepatic microsomal enzymes, including:

- Ciprofloxacin
- Corticosteroids
- Digitalis glycosides
- Itraconazole
- Ketoconazole
- Phenobarbital
- Phenylbutazone
- Warfarin

(rifampin causes induction of hepatic enzymes in dogs, mice, rabbits, pigs and rats; 29 potentially increasing metabolism and thereby decreasing serum concentrations of the above medications; there is some selectivity in enzyme induction so that not every drug that is oxidized by the system is affected; in guinea pigs and rats, hepatic metabolism does not appear to be significantly induced by commonly administered dosages of rifampin but can be by extremely high doses; phenobarbital will also increase the metabolism of rifampin by enzyme induction)

Human drug interactions and/or related problems

In addition to the above drug interactions reported in animals, the following drug interactions have been reported in humans, and are included in the human monograph Rifampin (Systemic) in USP DI Volume I. These drug interactions are intended for informational purposes only and may or may not be applicable to the use of rifampin in the treatment of animals:

- Aminophylline or Oxtriphylline or Theophylline (rifampin may increase metabolism of theophylline, oxtriphylline, and aminophylline by induction of hepatic microsomal enzymes, resulting in increased theophylline clearance)
- Anesthetics, hydrocarbon inhalation, except isoflurane (chronic use of hepatic enzyme-inducing agents prior to anesthesia, except isoflurane, may increase anesthetic metabolism, leading to increased risk of hepatotoxicity)
- Antiocoagulants, coumarin- or indandione-derivative (concurrent use with rifampin may enhance the metabolism of these antiocoagulants by induction of hepatic microsomal enzymes, resulting in a considerable decrease in the activity and effectiveness of the antiocoagulants; prothrombin time determinations may be required as frequently as once a day; dosage adjustments of antiocoagulants may be required before and after rifampin therapy)
- Azole antifungals (concurrent use may increase the metabolism of the azole antifungals, lowering their plasma concentrations; depending on the clinical situation, the dose of an azole antifungal may need to be increased during concurrent use with rifampin)
- Barbiturates (concurrent use with rifampin may enhance the metabolism of hexobarbital by induction of hepatic microsomal enzymes, resulting in lower serum concentrations; there are conflicting data on rifampin’s effect on phenobarbital; dosage adjustment may be required)
- Beta-adrenergic blocking agents, systemic (concurrent use of metoprolol or propranolol with rifampin has resulted in reduced plasma concentrations of these two beta-adrenergic blocking agents due to enhanced metabolism of hepatic microsomal enzymes by rifampin; although not documented, other beta-adrenergic blocking agents may also interact with rifampin)
- Bone marrow depressants (concurrent use of bone marrow depressants with rifampin may increase the leukopenic and/or thrombocytopenic effects; if concurrent use is required, close observation for myelotoxic effects should be considered)
- Chloramphenicol (concurrent use with rifampin may enhance the metabolism of chloramphenicol by induction of hepatic microsomal enzymes, resulting in significantly lower serum chloramphenicol concentrations; dosage adjustment may be necessary)
- Clofazimine

© 2007 The United States Pharmacopeial Convention All rights reserved
Concurrent use with rifampin has resulted in reduced absorption of rifampin, delaying its time to peak concentration, and increasing its half-life.

Corticosteroids, glucocorticoid and mineralocorticoid (concurrent use with rifampin may enhance the metabolism of corticosteroids by induction of hepatic microsomal enzymes, resulting in a considerable decrease in corticosteroid plasma concentrations; dosage adjustment may be required; rifampin has also counteracted endogenous cortisol and produced acute adrenal insufficiency in patients with Addison’s disease)

Cyclosporine (rifampin may enhance metabolism of cyclosporine by induction of hepatic microsomal enzymes and intestinal cytochrome P450 enzymes; dosage adjustment may be required)

Dapsone (concurrent use with rifampin may decrease the effect of dapsone because of increased metabolism resulting from stimulation of hepatic microsomal enzyme activity; dapsone concentrations may be decreased by half; dapsone dosage adjustments are not required during concurrent therapy with rifampin for leprosy)

Diazepam (concurrent use with rifampin may enhance the elimination of diazepam, resulting in decreased plasma concentrations; whether this effect applies to other benzodiazepines has not been determined; dosage adjustment may be necessary)

Disopyramide or Mexiletine or Propafenone or Quinidine or Tocainide (concurrent use with rifampin may enhance the metabolism of these antiarrhythmics by induction of hepatic microsomal enzymes, resulting in significantly lower serum antiarrhythmic concentrations; serum antiarrhythmic concentrations should be monitored and dosage adjustment may be necessary)

Estramustine or Estrogens (concurrent use of estramustine or estrogens with rifampin may result in significantly reduced estrogenic effect because of stimulation of estrogen metabolism or reduction in enterohepatic circulation of estrogens)

Hepatotoxic medications, other (concurrent use of rifampin and other hepatotoxic medications may increase the potential for hepatotoxicity; patients should be monitored closely for signs of hepatotoxicity)

Isoniazid (concurrent use of isoniazid with rifampin may increase the risk of hepatotoxicity, especially in patients with preexisting hepatic function impairment and/or in fast acetylators of isoniazid; patients should be monitored closely for signs of hepatotoxicity during the first 3 months of therapy)

Phenytoin (concurrent use with rifampin may stimulate the hepatic metabolism of phenytoin, increasing its elimination and thus counteracting its anticonvulsant effects; careful monitoring of serum hydantoin concentrations and dosage adjustments may be necessary before and after rifampin therapy)

Probencid (may compete with rifampin for hepatic uptake when used concurrently, resulting in increased and more prolonged rifampin serum concentrations and/or toxicity; however, the effect on rifampin serum concentrations is inconsistent, and concurrent use of probenecid to increase rifampin serum concentrations is not recommended)

Trimethoprim (concurrent use with rifampin may significantly increase elimination and shorten the elimination half-life of trimethoprim)

Verapamil, oral (rifampin has been found to accelerate the metabolism of oral doses of verapamil, resulting in a significant decrease in serum verapamil concentration, and thereby reversing its cardiovascular effects; concurrent use of intravenous verapamil with rifampin was found to have only minor effects on verapamil’s clearance and no significant effect on cardiovascular effects)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)—not necessarily inclusive (+ = major clinical significance):

With diagnostic test results

- Indocyanine green and Sulfobromophthalein sodium excretion test (BSP) (in rats, plasma clearances of indocyanine green and sulfobromophthalein sodium were increasingly and significantly delayed after 200 mg per kg of body weight a day was administered for 1 to 7 days; the impact of recommended doses, such as 20 mg/kg a day, on these excretion tests has not been measured)

- With physiology/laboratory test values
  - Alkaline phosphatase
    - (in the dog, mild increases in serum alkaline phosphatase levels are common and are not considered significant unless accompanied by elevations in other hepatic enzymes)
  - Dexamethasone suppression test (rifampin may prevent the inhibitory action of a standard dexamethasone dose administered for the overnight suppression test, rendering the test abnormal; it is recommended that rifampin therapy be discontinued 15 days before administering the dexamethasone suppression test)
  - Folate determinations, serum and Vitamin B12; determinations, serum (therapeutic concentrations of rifampin may interfere with standard microbiological assays for serum folate and vitamin B12; alternate methods must be considered when determining serum folate and vitamin B12 concentrations in patients taking rifampin)

- sulfobromophthalein (BSP) uptake and excretion (hepatic uptake and excretion of BSP in liver function tests may be delayed by rifampin, resulting in BSP retention; the

Human laboratory value alterations

The following laboratory value alterations have been reported in humans, and are included in the human monograph Rifampin (Systemic) in the USP DI Volume I; these laboratory value alterations are intended for informational purposes only and may or may not be applicable to the use of rifampin in the treatment of animals:

- With diagnostic test results
  - Coombs’ (antiglobulin) tests, direct (may become positive rarely during rifampin therapy)
  - Dexamethasone suppression test (rifampin may prevent the inhibitory action of a standard dexamethasone dose administered for the overnight suppression test, rendering the test abnormal; it is recommended that rifampin therapy be discontinued 15 days before administering the dexamethasone suppression test)
  - Folate determinations, serum and Vitamin B12; determinations, serum (therapeutic concentrations of rifampin may interfere with standard microbiological assays for serum folate and vitamin B12; alternate methods must be considered when determining serum folate and vitamin B12 concentrations in patients taking rifampin)

- sulfobromophthalein (BSP) uptake and excretion (hepatic uptake and excretion of BSP in liver function tests may be delayed by rifampin, resulting in BSP retention; the

© 2007 The United States Pharmacopeial Convention

All rights reserved
BSP test should be performed prior to the daily dose of rifampin to avoid false-positive test results. Urinalyses based on spectrometry or color reaction (rifampin may interfere with urinalyses that are based on spectrometry or color reaction due to rifampin’s reddish-orange to reddish-brown discoloration of urine).

With physiology/laboratory test values:
- Alanine aminotransferase (ALT [SGPT]) and Aspartate aminotransferase (AST [SGOT]) (values may be increased)
- Bilirubin, serum and Blood urea nitrogen (BUN) and Uric acid, serum (concentrations may be increased)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)—not necessarily inclusive (≠ = major clinical significance).

Risk-benefit should be considered when the following medical problem exists:

- Hepatic function impairment, severe (in dogs, hepatic function impairment may predispose to major side effects, and the risk should be carefully considered; in any species, dosage adjustments may be necessary with hepatic dysfunction and avoiding use of rifampin should be considered)[R-4]

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; ≠ = major clinical significance):
- Hepatic enzyme tests (particularly in dogs, hepatic enzymes should be monitored during rifampin therapy)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

- Diarrhea, self-limiting—often occurs in the first week of therapy and resolves without treatment[R-34]
- Hepatotoxicity[R-4]
- Sweating, mild to moderate—may occur with parenteral administration, more prominent with intravenous administration[R-13; 14]

Horses

- Sweating, mild to moderate—may occur with parenteral administration, more prominent with intravenous administration[R-13; 14]

Human side/adverse effects[R-6; 79]

In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans, and are included in the human monograph Rifampin (Systemic) in USP DI Volume I; these side/adverse effects are intended for informational purposes only and may or may not be applicable to the use of rifampin in the treatment of animals:

Incidence more frequent
- Gastrointestinal disturbances; reddish-orange to reddish-brown discoloration of urine, feces, saliva, sputum, sweat, and tears

Incidence less frequent
- Flulike syndrome (chills; difficult breathing; dizziness; fever; headache; muscle and bone pain; shivering); fungal overgrowth; hypersensitivity

Incidence rare
- Blood dyscrasias; hepatitis; hepatitis prodromal symptoms; interstitial nephritis

Note: Intermittent use of rifampin may increase the chance of a patient developing the flu-like syndrome, as well as acute hemolysis or renal failure. These reactions are thought to be immunologically mediated, and intermittent use of the medication should be limited to those conditions in which its safety and efficacy have been established.

Overdose

For more information in the case of overdose or unintentional ingestion, contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center (888-426-4435 or 900-443-0000; a fee may be required for consultation) and/or the manufacturer.

LD₅₀

The lethal dose for 50% of test animals (LD₅₀) is approximately 885 mg per kg of body weight (mg/kg) in the mouse, 1720 mg/kg in the rat, and 2120 mg/kg in the rabbit.[R-2]

Clinical effects of overdose

In human beings, overdose can cause mental changes, nausea and vomiting, angioedema, generalized pruritus, and red-orange discoloration of the mucous membranes, sclera, and skin.[R-63]

Signs of overdose specific to animals are not known.

Treatment of overdose

From the human therapeutic literature:[R-2; 63]

To decrease absorption—
- Evacuating stomach contents using ipecac syrup or gastric lavage.
- Administering an activated charcoal slurry to help adsorb residual rifampin in the gastrointestinal tract.
- Supportive therapy.

Client Consultation

Notify your veterinarian of any medications your animal is already receiving before treatment or any medications that may be initiated during treatment with rifampin because drug interactions can occur.[R-6] It is important to be sure that the animal receives the full course of treatment prescribed. However, if new signs occur, such as decreased appetite, depression, diarrhea, or jaundice,[R-13; 14; 34] contact your veterinarian.
Reddish-orange to reddish-brown discoloration of urine, stools, saliva, sputum, sweat, and tears may occur as a typical effect of the medication, but is not harmful. [R-63; 64]

**General Dosing Information**

The National Committee for Clinical Laboratory Standards (NCCLS) in the United States lists minimum inhibitory concentration (MIC) breakpoints of animal isolates for rifampin as ≤ 1 mcg/mL for susceptible organisms and ≥ 4 mcg/mL for resistant organisms. [R-8] Organisms testing between these values are considered intermediate and may or may not be inhibited. [R-8]

Specifically for *Rhodococcus equi*, one study of nine strains found minimum inhibitory concentration (MICs) for rifampin to be 0.0078 to 0.0625 mcg/mL. [R-14] In another study, a MIC of less than or equal to 0.25 mcg/mL was found for 18 *Rhodococcus equi* isolates; [R-7] 83% of these isolates had an MIC of 0.0625 or less. [R-7]

Other equine organisms have also been found to have MICs of less than 0.25 mcg/mL, including coagulase-positive *Staphylococcus* species (MIC of 0.0625 or less), *Streptococcus zoosporidemicus* (MIC of 0.0625 or less), *S. equisimilis* (MIC of 0.125 or less), and *Corynebacterium pseudotuberculosis* (MIC of 0.0156 or less). [R-7; 8] Gram-negative organisms have been found to be variably susceptible or resistant. [R-7; 8]

The MICs of 19 *Actinobacillus* isolates from horses ranged from 1 to 4 mcg/mL. [R-7]

The possibility of mixed infections involving both gram-positive and gram-negative organisms should be considered in some situations, such as young horses with respiratory tract infections. [R-7; 8] Because nonenteric gram-negative organisms can have variable susceptibility, susceptibility data should be used to determine the appropriate therapy. [R-7; 8]

The possibility of mixed infections and the rapid rise of resistance to rifampin make combination therapy the most logical recourse in many cases. [R-7] Rifampin has been shown in *in vitro* tests to have synergistic activity with erythromycin or trimethoprim and to have an additive effect with ampicillin or penicillin. [R-7; 8; 9; 10] However, rifampin’s activity in *in vitro* tests can be antagonistic to those of other antimicrobials, such as gentamicin; [R-10] it is not certain how this interaction might affect in vivo activity.

For oral dosage forms only

Administration with food reduces the rate of absorption and prolongs the time to peak concentration in adult horses. [R-4]

**Oral Dosage Forms**

Note: Rifampin is not specifically approved for veterinary use. In other USP information monographs the [R-15] and [R-16] designations indicate uses that are not included in U.S. and Canadian product labeling; however, in this monograph they reflect the lack of veterinary products and, therefore, product labeling.

**RIFAMPIN CAPSULES USP**

**Usual dose:**

- **Pneumonia, *Rhodococcus equi***: 5 mg per kg of body weight every twelve hours in combination with 25 mg of erythromycin estolate or erythromycin ethylsuccinate per kg of body weight every six to eight hours. [R-34; 36] Therapy may be continued for four to nine weeks or until radiographs and complete blood counts are normal. [R-11; R-46]

- **Potomac horse fever—Horses:** Oral, 10 mg per kg of body weight every twelve hours in combination with 25 mg of erythromycin estolate or erythromycin ethylsuccinate per kg of body weight every twelve hours. [R-11]

Note: [R-15; R-16; R-24] Horses—Although the safety and efficacy of rifampin have not been established, an oral dose of 10 mg rifampin per kg of body weight every twelve hours has been used in the treatment of susceptible bacterial infections, such as *staphylococcal infections* in horses, based on pharmacokinetic data. [R-6; 7] It is usually administered in combination with another antimicrobial, such as erythromycin or penicillin. [R-11; R-6; 7]

**Packaging and storage:** Store below 40 °C (104 °F), in a tight container, unless otherwise specified by the manufacturer. [R-2; 3]

**Preparation of dosage form:** Human product labeling suggests the preparation of an extemporaneous oral 1% w/v suspension with preprepared syrups when necessary. [R-2]

**USP requirements:** Preserve in tight, light-resistant containers, protected from excessive heat. Contain the labeled amount, within ±10%. Meet the requirements for Identification, Dissolution (75% in 45 minutes in 0.1 N hydrochloric acid in Apparatus 1 at 100 rpm), Uniformity of dosage units, and Loss on drying (not more than 3.0%). [R-3]

© 2007 The United States Pharmacopeial Convention

All rights reserved
Parenteral Dosage Forms
Note: Rifampin is not specifically approved for veterinary use. In other USP information monographs the US and CAN designations indicate uses that are not included in U.S. and Canadian product labeling; however, in this monograph they reflect the lack of veterinary products and, therefore, product labeling.

RIFAMPIN FOR INJECTION USP
Note: Although parenteral pharmacokinetic studies have been performed in horses and sheep, rifampin is generally administered by the oral route in animals. See RIFAMPIN CAPSULES USP; however, also note that oral dosing for horses is adjusted for poor bioavailability. Use of an oral dose for parenteral administration of rifampin could result in overdosage. Parenteral rifampin should be administered only by the intravenous route, not intramuscularly or subcutaneously. Extra-label withdrawal times—U.S. and Canada: The use of rifampin in food-producing animals has not been approved by the Food and Drug Administration or the Canadian Health Protection Branch; therefore, there are no established withdrawal times.

Strength(s) usually available:
U.S.—
Veterinary-labeled product(s): Not commercially available.
Human-labeled product(s):
600 mg (Rx) [Rifadin IV].
Canada—
Veterinary-labeled product(s): Not commercially available.
Human-labeled product(s): Not commercially available.

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a tight container, unless otherwise specified by the manufacturer. Protect from light.

Preparation of dosage form: Human product labeling recommends that 600 mg of rifampin powder be reconstituted with 10 mL of sterile water for injection to produce a 60 mg per mL (mg/mL) solution.

Prior to intravenous infusion, the amount calculated for administration may be used with a slight reduction in stability. Dextrose 5% for Injection is recommended for infusion medium, but sterile saline otherwise specified by the manufacturer. Protect from light.

Stability: The reconstituted 60 mg/mL solution is stable for 24 hours at room temperature. Once mixed with infusion medium to produce a 100 mL or 500 mL solution, the product should be administered within 4 hours; precipitation of rifampin may occur after this time.

USP requirements: Preserve in Containers for Sterile Solids. Contains the labeled amount, within −10% to +15%. Meets the requirements for Identification, Bacterial endotoxins, Sterility, pH (7.8–8.8, in a solution containing 60 mg of rifampin per mL), Water (not more than 1.0%), and Particulate matter.


