

POTENTIATED SULFONAMIDES (Veterinary—Systemic)

This monograph includes information on the following: Ormetoprim and Sulfadimethoxine; Pyrimethamine and Sulfadiazine†; Pyrimethamine and Sulfaquinoxaline*; Sulfadiazine and Trimethoprim; Sulfadoxine and Trimethoprim*; Sulfamethoxazole and Trimethoprim.

Some commonly used *brand names* are:

For veterinary-labeled products—

<i>Borgal</i> [Sulfadoxine and Trimethoprim]	<i>Romet-30</i> [Ormetoprim and Sulfadimethoxine]
<i>Novovet TMPS</i> [Sulfadoxine and Trimethoprim]	<i>Sulfaquinoxaline-S</i> [Pyrimethamine and Sulfaquinoxaline]
<i>Potensulf</i> [Sulfadoxine and Trimethoprim]	<i>Tribriksen 24%</i> [Sulfadiazine and Trimethoprim]
<i>Primor 120</i> [Ormetoprim and Sulfadimethoxine]	<i>Tribriksen 48%</i> [Sulfadiazine and Trimethoprim]
<i>Primor 240</i> [Ormetoprim and Sulfadimethoxine]	<i>Tribriksen 400 Oral Paste</i> [Sulfadiazine and Trimethoprim]
<i>Primor 600</i> [Ormetoprim and Sulfadimethoxine]	<i>Tribriksen 40% Powder</i> [Sulfadiazine and Trimethoprim]
<i>Primor 1200</i> [Ormetoprim and Sulfadimethoxine]	<i>Trimidox</i> [Sulfadoxine and Trimethoprim]
<i>Quinoxine-S</i> [Pyrimethamine and Sulfaquinoxaline]	<i>Trivetrin</i> [Sulfadoxine and Trimethoprim]
<i>Rebalance</i> [Pyrimethamine and Sulfadiazine]	<i>Tucoprim</i> [Sulfadiazine and Trimethoprim]
<i>Rofenaid 40</i> [Ormetoprim and Sulfadimethoxine]	<i>Uniprim</i> [Sulfadiazine and Trimethoprim]
<i>Romet 30</i> [Ormetoprim and Sulfadimethoxine]	

For human-labeled products—

<i>Apo-Sulfatrim</i> [Sulfamethoxazole and Trimethoprim]	<i>Septa</i> [Sulfamethoxazole and Trimethoprim]
<i>Apo-Sulfatrim DS</i> [Sulfamethoxazole and Trimethoprim]	<i>Septa DS</i> [Sulfamethoxazole and Trimethoprim]
<i>Bactrim</i> [Sulfamethoxazole and Trimethoprim]	<i>Septa Grape Suspension</i> [Sulfamethoxazole and Trimethoprim]
<i>Bactrim DS</i> [Sulfamethoxazole and Trimethoprim]	<i>Septa Suspension</i> [Sulfamethoxazole and Trimethoprim]
<i>Novo-Trimel</i> [Sulfamethoxazole and Trimethoprim]	<i>Sulfatrim Suspension</i> [Sulfamethoxazole and Trimethoprim]
<i>Novo-Trimel D.S.</i> [Sulfamethoxazole and Trimethoprim]	

Note: For a listing of dosage forms and brand names by country availability, see the *Dosage Forms* section(s).

*Not commercially available in the U.S.

†Not commercially available in Canada.

Category: Antibacterial (systemic); antiprotozoal (systemic).

Indications

Note: The text between ^{ELUS} and ^{EL} describes uses that are not included in U.S. product labeling. Text between ^{ELCAN} and ^{EL} describes uses that are not included in Canadian product labeling.

The ^{ELUS} or ^{ELCAN} designation can signify a lack of product availability in the country indicated. See the *Dosage Forms* section of this monograph to confirm availability.

General considerations

The combined and synergistic activities of the two agents in each type of potentiated sulfonamide produce antibacterial activity against a wide range of infections caused by gram-positive and gram-negative bacteria, some protozoa, and some anaerobes under certain conditions.^(R-44) The minimum inhibitory concentrations against specific susceptible bacteria for each antibiotic are generally lowered when the antibiotics are administered in the potentiated sulfonamide combination. The resistance developed to the potentiated sulfonamides is lower than that to each individual agent;^(R-20; 23) this is an important benefit because of the common resistance to sulfonamides and rapid development of resistance to diaminopyrimidines when used alone.^(R-20) Cross-resistance between sulfonamides is considered complete and often occurs between pyrimidines, as well.^(R-25; 94)

Accepted

^{ELUS}Arthritis, bacterial (treatment)^{EL}—*Pigs*: Sulfadoxine and trimethoprim injection is indicated in the treatment of bacterial arthritis caused by susceptible organisms.^(R-13-15)

Coccidiosis (prophylaxis)—

Chickens: ^{ELCAN}Ormetoprim and sulfadimethoxine Type A medicated article^{EL(R-6)} is indicated in the prevention of coccidiosis caused by susceptible *Eimeria acervulina*, *E. brunetti*, *E. maxima*, *E. mivati*, *E. necatrix*, and *E. tenella*.^{ELUS}Pyrimethamine and sulfaquinoxaline oral solution is indicated in the prevention of coccidiosis, caused by susceptible organisms.^{EL(R-17)}

^{ELCAN}*Partridges*, *chukar*^{EL}: Ormetoprim and sulfadimethoxine Type A medicated article is indicated in the prevention of coccidiosis caused by susceptible *Eimeria kofoidi* and *E. legionensis*.^(R-6; 125)

Turkeys: ^{ELCAN}Ormetoprim and sulfadimethoxine Type A medicated article^{EL} is indicated in the prevention of coccidiosis caused by susceptible *Eimeria adenoides*, *E. gallopavonis*, and *E. meleagridis*.^(R-6) ^{ELUS}Pyrimethamine and sulfaquinoxaline oral solution is indicated in the prevention of coccidiosis caused by susceptible organisms.^{EL(R-17)}

^{ELUS}Coccidiosis (treatment)^{EL}—*Chickens* and *turkeys*: Pyrimethamine and sulfaquinoxaline oral solution is indicated to aid in the treatment of susceptible coccidia.^(R-17)

^{ELCAN}Colibacillosis (prophylaxis)^{EL}—*Chickens*, broiler and replacement, and *ducks*: Ormetoprim and sulfadimethoxine Type A medicated article is indicated in the prevention of colibacillosis caused by susceptible *Escherichia coli*.^(R-6)

Colibacillosis (treatment)—

^{ELUS}*Cattle*^{EL}: Sulfadoxine and trimethoprim injection is indicated in the treatment of colibacillosis caused by susceptible organisms.^(R-13; 14)

^{ELCAN}*Ducks*^{EL}: Ormetoprim and sulfadimethoxine Type A medicated article is indicated in the control of colibacillosis caused by susceptible *E. coli*.^(R-6)

^{ELUS}*Pigs*^{EL}: Sulfadoxine and trimethoprim injection is indicated in the treatment of neonatal colibacillosis caused by susceptible *E. coli*.^(R-13; 14)

^{ELCAN}Enteric septicemia (treatment)^{EL}—*Catfish*: Ormetoprim and sulfadimethoxine Type A medicated article is indicated in the control of enteric septicemia caused by susceptible *Edwardsiella ictaluri*.^(R-7; 16)

^{ELUS}Enteritis, bacterial (treatment)^{EL}—

- Cattle:** Sulfadoxine and trimethoprim injection is indicated in the treatment of enteritis caused by susceptible *E. coli* or *Salmonella*.^{R-13; 14}
- Pigs:** Sulfadoxine and trimethoprim injection is indicated in the treatment of post-weaning scours caused by susceptible *E. coli*.^{R-13; 14}
- ^{ELCAN}**Equine protozoal myeloencephalitis (treatment)^{EL}—Horses:** Pyrimethamine and sulfadiazine oral suspension is indicated in the treatment of equine protozoal myeloencephalitis caused by *Sarcosystis neurona*.^{R-10; 110}
- ^{ELCAN}**Fowl cholera (prophylaxis)^{EL}—Chickens and turkeys:** Ormetoprim and sulfadimethoxine Type A medicated article is indicated in the prevention of fowl cholera caused by susceptible *Pasteurella multocida*.^{R-6}
- ^{ELCAN}**Fowl cholera (treatment)^{EL}—Ducks:** Ormetoprim and sulfadimethoxine Type A medicated article is indicated in the control of fowl cholera caused by susceptible *Pasteurella multocida*.^{R-6}
- Furunculosis (treatment)—Salmon and trout:** Ormetoprim and sulfadimethoxine Type A medicated article is indicated in the control of furunculosis caused by susceptible *Aeromonas salmonicida*.^{R-7; 16}
- ^{ELUS}**Gastrointestinal tract infections, bacterial (treatment)^{EL}—Cats and dogs:** Treatment of gastroenteritis with antimicrobials should rely on a specific diagnosis and knowledge of pathogen susceptibility. Sulfadiazine and trimethoprim injection is indicated in the treatment of acute gastrointestinal tract infections.^{R-8}
- ^{ELCAN}**Infectious coryza (prophylaxis)^{EL}—Chickens:** Ormetoprim and sulfadimethoxine Type A medicated article is indicated in the prevention of infectious coryza caused by susceptible *Haemophilus gallinarum*.^{R-6}
- ^{ELUS}**Mastitis (treatment)^{EL};** or
- ^{ELUS}**Metritis (treatment)^{EL}—Sows:** Sulfadoxine and trimethoprim injection is indicated in the treatment of mastitis-metritis-agalactia syndrome caused by susceptible organisms.^{R-13-15}
- ^{ELCAN}**New duck disease (treatment)^{EL}—Ducks:** Ormetoprim and sulfadimethoxine Type A medicated article is indicated in the control of new duck disease (infectious serositis) caused by susceptible *Riemerella anatipestifer*.^{R-6}
- ^{ELUS}**Perioperative infections (treatment)^{EL}—Horses:** Sulfadiazine and trimethoprim injection is indicated in the treatment of postoperative bacterial infections caused by susceptible organisms.^{R-9}
- ^{ELUS}**Pneumonia, bacterial (treatment)^{EL}—**
- Cattle:** Sulfadoxine and trimethoprim injection is indicated in the treatment of bacterial pneumonia, including bovine pneumonic pasteurellosis (shipping fever), caused by susceptible organisms.^{R-13; 14}
- Pigs:** Sulfadoxine and trimethoprim injection is indicated in the treatment of bacterial pneumonia caused by susceptible organisms.^{R-14; 15}
- ^{ELUS}**Pododermatitis (treatment)^{EL}—Cattle:** Sulfadoxine and trimethoprim injection is indicated in the treatment of pododermatitis caused by susceptible organisms.^{R-13; 14}
- Respiratory tract infections, bacterial (treatment)—**
- ^{ELUS}**Cats and dogs^{EL}:** Sulfadiazine and trimethoprim injection is indicated in the treatment of acute bacterial respiratory tract infections caused by susceptible organisms.^{R-8}
- Horses:** ^{ELUS}Sulfadiazine and trimethoprim injection^{EL}, ^{ELCAN}oral paste^{EL},^{R-3} and oral powder^{R-4; 11} are indicated in the treatment of respiratory tract infections caused by susceptible organisms.
- ^{ELUS}**Septicemia (treatment)^{EL}—Cattle:** Sulfadoxine and trimethoprim injection is indicated in the treatment of septicemia caused by susceptible organisms.^{R-13; 14}
- Skin and soft tissue infections (treatment)—**
- ^{ELUS}**Cats^{EL}:** Sulfadiazine and trimethoprim injection is indicated in the treatment of bacterial infections, such as abscesses and wounds, caused by susceptible organisms.^{R-8}
- Dogs:** ^{ELCAN}Ormetoprim and sulfadimethoxine tablets^{EL} are indicated in the treatment of skin and soft tissue infections caused by susceptible *E. coli* and *Staphylococcus intermedius*.^{R-5} ^{ELUS}Sulfadiazine and trimethoprim injection^{EL} is indicated in the treatment of abscesses and infected wounds caused by susceptible organisms.^{R-8}
- Horses:** ^{ELUS}Sulfadiazine and trimethoprim injection^{EL}, ^{ELCAN}oral paste^{EL},^{R-3} and oral powder^{R-4; 11} are indicated in the treatment of abscesses and infected wounds caused by susceptible organisms.
- Strangles (treatment)—Horses:** ^{ELUS}Sulfadiazine and trimethoprim injection^{EL}, ^{ELCAN}oral paste^{EL},^{R-3} and oral powder^{R-4; 11} are indicated in the treatment of acute strangles caused by susceptible organisms.
- Urinary tract infections (treatment)—Dogs:** Ormetoprim and sulfadimethoxine tablets are indicated in the treatment of acute urinary tract infections caused by susceptible organisms.^{R-5}
- ^{ELCAN}**Urogenital tract infections (treatment)^{EL}—Horses:** Sulfadiazine and trimethoprim oral paste and oral powder are indicated in the treatment of acute urogenital tract infections.^{R-3; 4}
- ^{ELUS}**Vibrio anguillarum infection^{EL}—Salmon:** Sulfadiazine and trimethoprim oral powder is indicated in the treatment of infections caused by susceptible *Vibrio anguillarum*.^{R-22; 64}

Potentially effective

- Bacterial infections (treatment)—Horses:** There are insufficient controlled studies to support the efficacy and safety of ^{ELUS,CAN}sulfamethoxazole and trimethoprim combination^{EL} in the treatment of bacterial infections in foals and horses; however, based on pharmacokinetic data, the combination is used in the treatment of susceptible infections.^{R-31-33}
- ^{ELUS,CAN}**Coccidiosis (treatment)^{EL}—Cats and dogs:** There are insufficient data to support the efficacy of sulfadiazine and trimethoprim or ormetoprim and sulfadimethoxine^{R-136} in the treatment of enteric coccidiosis in cats and dogs; however, these medications are used to reduce the shedding of oocysts and may aid in the natural elimination of *Isospora* species.
- ^{ELUS,CAN}**Equine infectious arthritis (treatment)^{EL}—Horses:** There are insufficient data to support the efficacy and safety of sulfadiazine and trimethoprim combination in the treatment of equine infectious arthritis; however, pharmacokinetic and clinical studies do lend support to its efficacy in the treatment of experimentally-induced *Staphylococcus aureus* joint infections.^{R-41; 42}
- ^{ELUS,CAN}**Equine protozoal myeloencephalitis (treatment)^{EL};** or
- ^{ELUS,CAN}**Protozoal infections (treatment)^{EL}—Horses:** There are insufficient controlled studies to support the efficacy and safety of sulfamethoxazole and trimethoprim combination in the treatment of protozoal infections in foals and horses; however, based on pharmacokinetic data and *in vitro* studies, the combination is used in the treatment of susceptible infections.^{R-31-33; 110} Prior to the availability of labeled products to treat equine protozoal myeloencephalitis, administration of sulfamethoxazole and trimethoprim in combination with pyrimethamine was clinically useful in treating horses with this disease.^{R-146}
- ^{ELUS,CAN}**Meningitis, bacterial (treatment)^{EL}—Dogs:** There are insufficient data to support the efficacy of sulfadiazine and trimethoprim combination in the treatment of bacterial meningitis in dogs; however, the combination is considered an alternative agent in the treatment of this indication. With the waning availability of sulfadiazine and trimethoprim dosage forms for dogs, a sulfonamide, such as sulfadimethoxine, or another potentiated sulfonamide combination, such as sulfamethoxazole and trimethoprim, may be considered when first choice antibiotics for this indication are not suitable. For dosage information, see *Sulfadiazine and Trimethoprim Injection in the Dosage Forms* section of this monograph. Blood-brain barrier penetration requires high dosages of potentiated sulfonamides and patients should be monitored for potential adverse effects.
- ^{ELUS,CAN}**Nocardiosis (treatment)^{EL}—Cats and dogs:** There are insufficient data to support the efficacy of sulfadiazine and trimethoprim or sulfamethoxazole and trimethoprim in the

treatment of nocardiosis in cats and dogs; however, these medications are used. Sulfonamides have been considered the treatment of choice and there is some evidence to suggest that sulfadiazine or sulfamethoxazole and trimethoprim are efficacious in the treatment of nocardiosis.^(R-128-133) Ormetoprim and sulfadimethoxine combination could also be effective in the treatment of nocardiosis, based on a pharmacokinetic profile similar to that of trimethoprim with sulfadiazine or sulfamethoxazole.^(R-138) Because of a variability in the susceptibility of *Nocardia* species, culture and sensitivity tests should be performed, if possible. Surgical drainage should be provided for any abscesses or draining tracts.^(R-130; 131) Sulfonamide and trimethoprim combination administered alone may not be effective in the treatment of cerebral nocardiosis.^(R-132)

^{ELUS,CAN}Pneumonia (treatment)^{EL}—*Calves*, preruminating: One of several medications labeled for this indication would be the first therapeutic choice in this food-producing species. In the United States, Animal Medicinal Drug Use Clarification Act (AMDUCA) regulations address this issue.^(R-147) At one time, Canadian sulfadiazine and trimethoprim boluses were labeled for use in the treatment of bacterial pneumonia in calves.^(R-12) Such a product has not been available in the United States. Although there are no sulfadiazine and trimethoprim products labeled for use in calves in the United States or Canada at this time, oral sulfadiazine and trimethoprim might be used in the treatment of susceptible infections, such as bacterial pneumonia in calves, if first choice medications were considered unlikely to be effective. For dosage information, see *Sulfadiazine and Trimethoprim Oral Paste* in the *Dosage Forms* section of this monograph.

^{ELUS,CAN}Prostate infection (treatment)^{EL}—*Dogs*: There are insufficient data to support the efficacy of trimethoprim in combination with sulfadiazine or sulfamethoxazole in the treatment of prostate infections caused by susceptible organisms in dogs; however, pharmacokinetic studies show that these trimethoprim and sulfonamide combinations are distributed into prostate fluid at therapeutic concentrations.^(R-48) Ormetoprim and sulfadimethoxine combination also could be effective in the treatment of prostatitis, based on a pharmacokinetic profile similar to that of trimethoprim with sulfadiazine or sulfamethoxazole.^(R-138)

Regulatory Considerations

U.S.—

Withdrawal times have been established for ormetoprim and sulfadimethoxine Type A medicated article (see the *Dosage Forms* section).

Canada—

Withdrawal times have been established for ormetoprim and sulfadimethoxine Type A medicated article; pyrimethamine and sulfaquinoxaline oral solution; sulfadiazine and trimethoprim oral powder; and sulfadoxine and trimethoprim injection (see the *Dosage Forms* section).

Chemistry

Chemical group:

Ormetoprim, pyrimethamine, and trimethoprim—
Diaminopyrimidines.

Sulfadiazine, sulfadimethoxine, sulfadoxine, sulfamethoxazole, and sulfaquinoxaline—Sulfonamides.

Chemical name:

Ormetoprim—2,4-Pyrimidinediamine, 5-[(4,5-dimethoxy-2-methylphenyl)methyl]-.^(R-1)

Pyrimethamine—2,4-Pyrimidinediamine, 5-(4-chlorophenyl)-6-ethyl-.^(R-1)

Sulfadiazine—Benzenesulfonamide, 4-amino-*N*-2-pyrimidinyl-.^(R-1)

Sulfadimethoxine—Benzenesulfonamide, 4-amino-*N*-(2,6-dimethoxy-4-pyrimidinyl)-.^(R-1)

Sulfadoxine—Benzenesulfonamide, 4-amino-*N*-(5,6-dimethoxy-4-pyrimidinyl)-.^(R-1)

Sulfamethoxazole—Benzenesulfonamide, 4-amino-*N*-(5-methyl-3-isoxazolyl)-.^(R-1)

Sulfaquinoxaline—*N*¹-2-Quinoxalinylsulfanilamide.^(R-1)

Trimethoprim—2,4-Pyrimidinediamine, 5-[(3,4,5-trimethoxyphenyl)methyl]-.^(R-1)

Molecular formula:

Ormetoprim—C₁₆H₁₈N₄O₂.^(R-1)

Pyrimethamine—C₁₂H₁₃ClN₄.^(R-1)

Sulfadiazine—C₁₀H₁₀N₄O₂S.^(R-1)

Sulfadimethoxine—C₁₂H₁₄N₄O₄S.^(R-1)

Sulfadoxine—C₁₂H₁₄N₄O₄S.^(R-1)

Sulfamethoxazole—C₁₀H₁₁N₃O₃S.^(R-1)

Sulfaquinoxaline—C₁₄H₁₂N₄O₂S.^(R-1)

Trimethoprim—C₁₄H₁₈N₄O₃.^(R-1)

Molecular weight:

Ormetoprim—274.32.^(R-1)

Pyrimethamine—248.71.^(R-1)

Sulfadiazine—250.28.^(R-1)

Sulfadimethoxine—310.33.^(R-1)

Sulfadoxine—310.33.^(R-1)

Sulfamethoxazole—253.28.^(R-1)

Sulfaquinoxaline—300.34.^(R-1)

Trimethoprim—290.32.^(R-1)

Description:

Ormetoprim—White powder.^(R-5)

Pyrimethamine USP—White, odorless, crystalline powder.^(R-117)

Sulfadiazine USP—White or slightly yellow powder. Odorless or nearly odorless and stable in air, but slowly darkens on exposure to light.^(R-117)

Sulfadimethoxine USP—Practically white, crystalline powder.^(R-117)

Sulfadoxine—White or yellowish-white crystalline powder, melting at 197–200 °C.^(R-118)

Sulfamethoxazole USP—White to off-white, practically odorless, crystalline powder.^(R-117)

Sulfaquinoxaline—Yellow, odorless powder.^(R-118)

Trimethoprim USP—White to cream-colored, odorless crystals, or crystalline powder.^(R-117)

pKa:

Sulfadiazine—6.4.^(R-25)

Sulfadimethoxine—6.2.^(R-97; 98)

Sulfadoxine—6.3.^(R-25)

Sulfamethoxazole—5.7.^(R-25)

Sulfaquinoxaline—5.5.^(R-99; 100)

Trimethoprim—7.6.^(R-73; 90)

Solubility:

Pyrimethamine USP—Practically insoluble in water; slightly soluble in acetone, in alcohol, and in chloroform.^(R-117)

Sulfadiazine USP—Practically insoluble in water; freely soluble in dilute mineral acids, in solutions of potassium and sodium hydroxides, and in ammonia TS; sparingly soluble in alcohol and in acetone; slightly soluble in human serum at 37 °C.^(R-117)

Sulfadimethoxine USP—Soluble in 2 *N* sodium hydroxide; sparingly soluble in 2 *N* hydrochloric acid; slightly soluble in alcohol, in ether, in chloroform, and in hexane; practically insoluble in water.^(R-117)

Sulfadoxine—Very slightly soluble in water; slightly soluble in alcohol and in methyl alcohol; practically insoluble in ether. Dissolves in solutions of alkali hydroxides and in dilute mineral acids.^(R-118)

Sulfamethoxazole USP—Practically insoluble in water, in ether, and in chloroform; freely soluble in acetone and in dilute solutions of sodium hydroxide; sparingly soluble in alcohol.^(R-117)

Sulfaquinoxaline—Practically insoluble in water; very slightly soluble in alcohol; practically insoluble in ether; freely soluble in aqueous solutions of alkalis.^(R-118)

Trimethoprim USP—Very slightly soluble in water; soluble in benzyl alcohol; sparingly soluble in chloroform and in

methanol; slightly soluble in alcohol and in acetone; practically insoluble in ether and in carbon tetrachloride.^[R-117]

Pharmacology/Pharmacokinetics

Note: Unless otherwise noted, pharmacokinetic values are based on administration of a single intravenous dose and concurrent administration of a diaminopyrimidine and a sulfonamide. When sulfamethoxazole and trimethoprim are administered concurrently to horses, the pharmacokinetics of each drug appears to be unaffected by the presence of the other.^[R-30; 32]

Mechanism of action/Effect:

Sulfonamides—The sulfonamides are bacteriostatic antimicrobials that interfere with the biosynthesis of folic acid in bacterial cells; they compete with para-aminobenzoic acid (PABA) for incorporation into dihydrofolic acid.^[R-20] By replacing the PABA molecule in dihydrofolic acid, they prevent formation of folic acid required for nucleic acid synthesis and multiplication of the bacterial cell.^[R-94; 101] Sulfonamides are effective only in cells that must produce their own folic acid; mammalian cells do not synthesize folic acid, but get it from outside sources.

Diaminopyrimidines—Ormetoprim and trimethoprim are bacteriostatic antimicrobials that block a step in folate production just subsequent to that affected by the sulfonamides.^[R-5; 23] Bacterial production of tetrahydrofolic acid from dihydrofolate is interrupted by the diaminopyrimidine as it reversibly binds and inhibits dihydrofolate reductase. Because the conversion of dihydrofolic acid to tetrahydrofolic acid is blocked, folate cannot be produced. Pyrimethamine causes the same inhibition of dihydrofolate reductase in protozoa.^[R-20] Like bacteria and protozoa, animal cells also reduce folic acid to tetrahydrofolic acid; however, bacterial and protozoal dihydrofolate reductase is significantly more tightly bound by trimethoprim than is human dihydrofolate reductase.

Potentiated sulfonamides—Because the diaminopyrimidines exert their effect on folate biosynthesis at a step immediately subsequent to the one at which the sulfonamides act, the combination of a sulfonamide and diaminopyrimidine produces a synergistic effect that deprives the cell of essential nucleic acids and proteins. The potentiated sulfonamide combination produces an antimicrobial effect that is bacteriostatic and sometimes bactericidal against certain bacteria under optimum conditions.^[R-23; 24] The minimal effective ratio of sulfonamide to diaminopyrimidine in the target tissue is 20 to 1 for synergism. At equimolar quantities, other ratios are equally effective, depending on the strain of organism and the minimum inhibitory concentration (MIC) for each drug. Therefore, 16 to 1, 10 to 1, and other ratios may be effective, but combinations are formulated to achieve at least 20 to 1 *in vivo*.^[R-20]

Absorption: Oral—

Ormetoprim and sulfadimethoxine:

Calves, 6 weeks of age—The bioavailability of oral ormetoprim is very poor in ruminating calves;^[R-86] the bioavailability of oral sulfadimethoxine in calves is slow but complete and unaffected by ruminant status.^[R-81]

Dogs—Ormetoprim and sulfadimethoxine are rapidly and well absorbed after oral administration.^[R-5]

Horses—Oral absorption of ormetoprim and sulfadimethoxine is variable. Sulfadimethoxine appears to be more efficiently absorbed than ormetoprim.^[R-35; 36]

Sulfadimethoxine administered alone: Bioavailability—

Catfish, channel: 40 mg/kg dose—^[R-68]

Free base: 31%.

Sodium salt: 34%.

Trout, rainbow:

42 mg/kg dose—^[R-67]

Free base: 34%.

Sodium salt: 63%.

126 mg/kg dose—Sodium salt: 50%.^[R-67]

Sulfadiazine and trimethoprim:

Calves, 6 weeks of age—The bioavailability of oral trimethoprim is greatly reduced in ruminating calves as compared to preruminating calves. Therapeutic serum concentrations (> 0.1 mcg/mL) were not achieved with oral administration of 25 mg of sulfadiazine and 5 mg of trimethoprim in combination to ruminating calves.^[R-81]

The absorption of oral sulfadiazine in calves is slow but complete and unaffected by rumen status.^[R-81]

Dogs—Sulfadiazine and trimethoprim are rapidly and well absorbed following oral administration.^[R-76] However, absorption can be variable among dogs and between different doses given to the same dog.^[R-46]

Horses—The absorption of trimethoprim is delayed when a horse has free access to feed.^[R-27] Initial serum concentrations will be lower in a fed horse than in a fasted horse; however, the effect is greatly decreased by the third day of treatment.^[R-27]

Pigs—Bioavailability: Dose of 40 mg of sulfadiazine and 4 mg of trimethoprim per kg—Fasted or fed:

Sulfadiazine—85 to 89%.^[R-91]

Trimethoprim—90 to 92%.^[R-91]

Sheep—Absorption of sulfadiazine in sheep is comparable to that in dogs; however, trimethoprim is not as well absorbed orally in sheep as in dogs.^[R-76]

Sulfamethoxazole and trimethoprim: Bioavailability—Quail:

Dose of 50 mg of sulfamethoxazole and 10 mg of

trimethoprim per kg of body weight—

Sulfamethoxazole: 81%.^[R-93]

Trimethoprim: 41%.^[R-93]

Distribution: Potentiated sulfonamides are widely distributed throughout body tissues.^[R-3] In general, the diaminopyrimidine concentration in plasma peaks early and is quickly found in high concentrations in tissues;^[R-76] therefore, concentrations are generally higher in the tissues than in the serum.^[R-25] The sulfonamide component generally is found at higher concentrations in plasma for a much longer time and tissue distribution is slower.^[R-76] Initial concentrations of sulfonamides in tissues are generally lower than those in plasma.^[R-25]

Calves, preruminating—Sulfadiazine and trimethoprim are distributed well into cerebrospinal fluid (CSF) and synovial fluid.^[R-79; 80]

Dogs—Potentiated sulfonamides are rapidly and widely distributed in the tissues. Trimethoprim and sulfadiazine are distributed into the aqueous and vitreous humors of the eye at concentrations that are 30 to 50% of serum concentrations.^[R-45] Trimethoprim is distributed into prostatic fluid at concentrations that are up to three times the serum concentration and are higher when trimethoprim is administered concurrently with sulfadiazine or sulfamethoxazole.^[R-48] Sulfadiazine and sulfamethoxazole are distributed into prostatic fluid at about 10% of the concurrent serum concentration.^[R-48]

Fish—Sulfadimethoxine administered alone:

In channel catfish, sulfadimethoxine is distributed into the muscle at the highest concentration immediately after administration, but within 48 to 96 hours the highest concentrations are in the bile.^[R-68] At any point in time there can be wide variation in tissue residues among fish.^[R-69]

In rainbow trout, sulfadimethoxine is distributed at the highest concentrations into the bile, followed by the intestine, liver, blood, skin, kidney, spleen, gill, muscle, and fat.^[R-67]

Horses—Distribution of potentiated sulfonamides has been

broadly investigated in the horse. Ormetoprim and sulfadimethoxine, sulfadiazine and trimethoprim, and sulfamethoxazole and trimethoprim are all well distributed into peritoneal fluid, CSF, synovial fluid, and urine.^[R-29; 31; 33; 35] Ormetoprim and sulfadimethoxine also have been shown to be well distributed into the endometrium.^[R-35]

Inflammation in the meninges or synovium does not significantly affect distribution into the respective fluids.^[R-31] Ormetoprim and sulfadimethoxine: Equine endometrial tissue and synovial and peritoneal fluid concentrations of ormetoprim were similar to concurrent serum concentrations and concentrations of sulfadimethoxine in those fluids were 25 to 30% of serum concentration.^[R-35]

Sulfadimethoxine and trimethoprim: After 4-day dosing in mares, trimethoprim was measured in CSF at 50% of serum concentrations, but sulfadimethoxine was measured at 2.7% of serum concentrations.^[R-35]

Sulfamethoxazole and trimethoprim: A single dose of 36 mg of sulfamethoxazole and 7.5 mg of trimethoprim per kg of body weight, administered intravenously to mares, reached concentrations in serum sufficient to exceed the minimum inhibitory concentrations (MICs) of common bacterial and protozoal pathogens.^[R-33] After repeated doses, sulfamethoxazole, unlike trimethoprim, accumulated in the CSF.^[R-31]

Volume of distribution (Vol_d):

Ormetoprim and sulfadimethoxine—*Horses*:^[R-35]

Ormetoprim—

Area: 1.7 Liters per kg (L/kg).

Steady state: 1.2 L/kg.

Sulfadimethoxine—

Area: 0.28 L/kg.

Steady state: 0.27 L/kg.

Sulfadiazine and trimethoprim—

Calves: Area—

Sulfadiazine:

1 day of age—0.72 L/kg.^[R-79]

1 week of age—0.66 L/kg.^[R-79; 80]

6 weeks of age—0.58 L/kg.^[R-79]

Ruminating—0.85 L/kg.^[R-77]

Trimethoprim:

1 day of age—1.69 L/kg.^[R-79]

1 week of age—2.2 to 2.5 L/kg.^[R-79; 80]

6 weeks of age—2.27 L/kg.^[R-79]

Ruminating—1.97 L/kg.^[R-77]

Horses: Steady state—

Sulfadiazine: 0.58 L/kg.^[R-43]

Trimethoprim: 1.68 L/kg.^[R-43]

Pigs: Steady state—

Sulfadiazine: 0.54 L/kg.^[R-91]

Trimethoprim: 1.8 L/kg.^[R-91]

Sulfadimethoxine administered alone—Steady state:

Catfish, channel—0.66 L/kg.^[R-68]

Trout, rainbow—0.42 to 0.5 L/kg.^[R-67; 70]

Sulfadoxine and trimethoprim—

Cows: Apparent—

Sulfadoxine: 0.37 L/kg.^[R-82]

Trimethoprim: 1.14 L/kg.^[R-82]

Goats: Apparent—

Sulfadoxine: 0.27 L/kg.^[R-72]

Trimethoprim: 1.2 L/kg.^[R-72]

Horses: Apparent—

Sulfadoxine: 0.39 L/kg.^[R-30]

Trimethoprim: 1.5 L/kg.^[R-30]

Sulfamethoxazole and trimethoprim—

Foals:

Sulfamethoxazole—Area and steady state: 0.73 L/kg.^[R-32]

Trimethoprim—Area and steady state: 2.2 L/kg.^[R-32]

Horses:

Sulfamethoxazole—

Area: 0.36 L/kg.^[R-31]

Steady state: 0.33 L/kg.^[R-31] 0.5 L/kg.^[R-33]

Trimethoprim—

Area: 2.27 L/kg.^[R-31]

Steady state: 1.62 L/kg.^[R-31] 2.79 L/kg.^[R-33]

Quail:

Sulfamethoxazole—Area: 0.48 L/kg.^[R-93]

Trimethoprim—Area: 3.9 L/kg.^[R-93]

Protein binding: In general, the binding of sulfonamides to proteins is concentration-dependent and trimethoprim protein binding is independent of plasma concentration.^[R-25; 30] There appears to be no interference in protein binding between sulfadoxine and trimethoprim;^[R-30] this may also be true for other potentiated sulfonamides.

Sulfadiazine—*Cattle*: 50% (concentration not specified).^[R-75]

Sulfadimethoxine—

Cats: 87.5% (50 mcg/mL plasma concentration).^[R-102]

Catfish, channel: 18%, not concentration-dependent.^[R-68]

Chickens: Average binding over a range of concentrations—

40%, at serum concentrations of 2 to 10 mcg/mL.^[R-103]

Dogs: > 75%, at plasma concentrations of 50 to 150 mcg/mL.^[R-104]

Goats: 94%, at plasma concentration of 100 micromole/L.^[R-98]

Trout, rainbow: 17%, not concentration-dependent.^[R-67]

Sulfadoxine—

Horses:

72%, at serum concentration of 50 mcg/mL.^[R-30]

40%, at serum concentration of 150 mcg/mL.^[R-30]

14%, at serum concentration of 450 mcg/mL.^[R-30]

Cows:

65 to 80%, at serum concentration of 100 mcg/mL or below.^[R-82; 83]

44 to 51%, at serum concentration of 150 mcg/mL or more.^[R-82; 83]

Trimethoprim—

Cows: 57%.^[R-83]

Goats: 48%.^[R-73]

Horses: 50%.^[R-30]

Pigs: 33 to 54%.^[R-90]

Biotransformation:

Sulfonamides—Sulfonamides are metabolized primarily in the liver, but metabolism also occurs in other tissues.

Biotransformation occurs by acetylation, glucuronide conjugation, and aromatic hydroxylation in many species.^[R-94]

The types of metabolites formed and the amount of each varies depending on the specific sulfonamide administered; the species, age, diet, and environment of the animal; the presence of disease; and, with the exception of pigs and ruminants, the gender of the animal.^[R-105-108] N₄-acetyl metabolites have no antimicrobial activity and hydroxymetabolites have 2.5 to 39.5% of the activity of the parent compound.^[R-109] Metabolites may compete with the parent drug for involvement in folic acid synthesis. They have little detrimental effect on the bacterial cell, so their presence could decrease the activity of the remaining parent drug.^[R-109]

Sulfadiazine—*Calves*: Sulfadiazine is excreted primarily as unchanged drug in the urine; the percentage of unchanged drug excreted increases from 1 day of age to 42 days of age, changing from 22 to 50%.^[R-79]

Sulfadimethoxine:

Catfish, channel—Metabolized primarily by the liver; acetylation is the major pathway.^[R-68]

Dogs—Sulfadimethoxine is not acetylated in the dog as it is in other species, and it is excreted primarily as unchanged drug in the dog.^[R-5]

Salmon—Metabolism occurs primarily in the liver.^[R-66]

Diaminopyrimidines—Trimethoprim: In many species, including

cows, goats, and pigs, trimethoprim is extensively metabolized.^(R-25; 79)

Half-life:

Absorption—*Horses*: Oral—Sulfadiazine and trimethoprim: Dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight (mg/kg)^(R-43)

Sulfadiazine: 0.35 hour.

Trimethoprim: 0.44 hour.

Distribution—*Horses*: Oral—Sulfadiazine and trimethoprim:

Dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight^(R-43)

Sulfadiazine: 0.27 hour.

Trimethoprim: 0.15 hour.

Elimination—

Ormetoprim and sulfadimethoxine: *Horses*—

Ormetoprim: 1.7 hours.^(R-35)

Sulfadimethoxine: 7.9 hours.^(R-35)

Sulfadiazine: Administered alone orally—*Dogs*: 9.84 hours.^(R-49)

Sulfadiazine and trimethoprim:

Calves—

1 day of age:

Sulfadiazine—5.7 hours.^(R-79)

Trimethoprim—8.4 hours.^(R-79)

1 week of age:

Sulfadiazine—4.4 hours.^(R-79; 80)

Trimethoprim—2.1 hours.^(R-79; 80)

6 weeks of age:

Sulfadiazine—3.6 hours.^(R-79)

Trimethoprim—0.9 hour.^(R-79)

Calves, ruminating—

Sulfadiazine: 3.25 hours,^(R-77) 4 hours.^(R-78)

Trimethoprim: 1 hour,^(R-78) 3.44 hours.^(R-77)

Horses—

Sulfadiazine: 2.7 hours,^(R-29) 4.65 hours,^(R-43) 7 hours.^(R-3)

Trimethoprim: 2 to 3 hours.^(R-29; 32; 43)

Sulfadimethoxine: Administered alone—

Cats: 10.2 hours.^(R-102)

Dogs: 13.1 hours.^(R-104)

Trout, rainbow: 16 hours.^(R-67; 70)

Sulfadoxine and trimethoprim:

Cows, lactating—

Sulfadoxine:

Alpha phase (up to 4 hours postadministration)—0.9 hour.^(R-82)

Beta phase (between 4 and 48 hours postadministration)—10.8 hours.^(R-82)

Trimethoprim: 1.18 hours.^(R-82)

Goats—

2 days of age:

Sulfadoxine—16.5 hours.^(R-72)

Trimethoprim—3 hours.^(R-72)

40 days of age to adult:

Sulfadoxine—11.7 hours.^(R-72)

Trimethoprim—0.8 hour.^(R-72)

Horses—

Sulfadoxine: 14 hours,^(R-30) 9.7 hours.^(R-37)

Trimethoprim: 3.2 hours,^(R-30) 1.9 hours.^(R-37)

Sheep—

1 week of age:

Sulfadoxine—15.3 hours.^(R-84)

Trimethoprim—2.5 hours.^(R-84)

4 months of age to adult:

Sulfadoxine—11.5 hours.^(R-84)

Trimethoprim—0.75 hour.^(R-74; 84)

Sulfamethoxazole and trimethoprim:

Horses—

Sulfamethoxazole: 3.5 hours,^(R-31) 4.8 hours.^(R-33)

Trimethoprim: 1.9 hours,^(R-31) 3.4 hours.^(R-33)

Horse foals—

Sulfamethoxazole: 9.9 hours.^(R-32)

Trimethoprim: 1.6 hours.^(R-32)

Pony foals—

Sulfamethoxazole: 5.8 hours.^(R-32)

Trimethoprim: 2.8 hours.^(R-32)

Quail:

Sulfamethoxazole—2.9 hours.^(R-93)

Trimethoprim—2.38 hours.^(R-93)

Trimethoprim: Administered alone—

Dogs: Based on oral dosing—2.5 hours.^(R-30; 49)

Pigs: 2.4 hours.^(R-89)

Peak serum concentration:

Sulfadimethoxine—Administered alone: Oral—

Catfish, channel: 7.83 to 11 mcg/mL at 3 to 6 hours (after 5 days of dosing 40 to 42 mg/kg every 24 hours).^(R-68; 69)

Chickens: 106.3 mcg/mL at 12 hours (single dose of 100 mg/kg).^(R-103)

Cows: 114 ± 10 mcg/mL at 10 hours (dose of 107 mg/kg).^(R-111)

Dogs: 67 ± 16 mcg/mL at 3.75 hours (dose of 55 mg/kg).^(R-104)

Ormetoprim and sulfadimethoxine—Oral:

Foals, 1 to 3 days of age—0.65 mcg of ormetoprim per mL at 2 hours and 54.6 mcg of sulfadimethoxine per mL at 8 hours (dose of 3.5 mg of ormetoprim and 17.5 mg of sulfadimethoxine per kg of body weight).^(R-36)

Horses—80 mcg of sulfadimethoxine per mL at 8 hours and 0.92 mcg of ormetoprim per mL at 0.5 hour postadministration (loading dose of 9.2 mg of ormetoprim and 45.8 mg of sulfadimethoxine per kg of body weight).^(R-25)

Sulfadiazine and trimethoprim—Oral:

Calves—

1 week of age: 11.9 mcg of sulfadiazine per mL at 12 hours and 0.41 mcg of trimethoprim per mL at 3 hours (dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg).^(R-81)

6 weeks of age:

Milk-fed—17.3 mcg of sulfadiazine per mL at 3 hours and 0.43 mcg of trimethoprim per mL at 1.5 hours (dose of 25 mg sulfadiazine and 5 mg of trimethoprim per kg of body weight).^(R-81)

Grain and fiber-fed—14.9 mcg of sulfadiazine per mL at 8 hours and < 0.1 mcg of trimethoprim per mL (below test limit) for entire trial (dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight).^(R-81)

Dogs—

12.4 mcg of sulfadiazine per mL at 4 hours and 1.7 mcg of trimethoprim per mL at 1 hour (dose of 20 mg of sulfadiazine and 4 mg of trimethoprim per kg of body weight).^(R-49)

30.1 mcg of sulfadiazine per mL and 1.52 mcg of trimethoprim per mL at 3 hours (dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight).^(R-19)

After 2 days of dosing every 12 hours: 67.4 mcg of sulfadiazine per mL and 2.98 mcg of trimethoprim per mL at 2 hours (dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg).^(R-46)

After 4 days of dosing every 24 hours: 84.7 mcg of sulfadiazine at 3 hours and 2.55 mcg of trimethoprim per mL at 2 hours (dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg).^(R-46)

Horses—

Fasted: 9 to 13 mcg of sulfadiazine per mL at 3 hours and 1 to 1.5 mcg of trimethoprim per mL at 1 to 2 hours

(dose of 25 to 29 mg of sulfadiazine and 5 to 6 mg of trimethoprim per kg of body weight).^(R-27-29)

Fed: 10 mcg of sulfadiazine per mL and 0.5 mcg of trimethoprim per mL at 6 hours (dose of 29.2 mg of sulfadiazine and 5.8 mg of trimethoprim per kg of body weight).^(R-27)

Pigs—

Fasted: 32 mcg of sulfadiazine per mL at 4.3 hours and 1.9 mcg of trimethoprim per mL at 2.1 hours (oral dose of 40 mg of sulfadiazine and 8 mg of trimethoprim per kg of body weight).^(R-91)

Fed: 25 mcg of sulfadiazine per mL at 3.2 hours and 1.5 mcg of trimethoprim per mL at 3.4 hours (oral dose of 40 mg of sulfadiazine and 8 mg of trimethoprim per kg of body weight).^(R-91)

Salmon—20.3 mcg of sulfadiazine per mL at 24 hours and 3.25 mcg of trimethoprim per mL at 12 hours (oral dose of 83.3 mg of sulfadiazine and 16.7 mg of trimethoprim per kg of body weight of fish at 8 °C).^(R-63)

Sulfadoxine and trimethoprim—Cattle: Intramuscular administration—30.3 mcg of sulfadoxine per mL at 2 hours and 0.7 mcg of trimethoprim per mL at 0.75 to 1 hour (dose of 13.3 mg of sulfadoxine and 2.7 mg of trimethoprim per kg of body weight).^(R-85)

Sulfamethoxazole and trimethoprim—Horses: Oral administration—0.26 mcg/mL of trimethoprim at 0.75 hour and 13.7 mcg/mL of sulfamethoxazole at 1.5 hours (dose of 12.5 mg of sulfamethoxazole and 2.5 mg of trimethoprim per kg of body weight).^(R-31)

Duration of action: Duration of action may be estimated by the length of time target serum concentrations are maintained; however, duration of action for the potentiated sulfonamides is difficult to estimate from target serum concentrations^(R-78) because of the rapid movement of the diaminopyrimidines into the tissues and the possibly wide range of local sulfonamide to diaminopyrimidine concentration ratios believed to be effective and synergistic. Target concentrations should be viewed as estimates only, and clinical response should be considered one of the measurements of activity of the medication. Some sources consider bacteria susceptible if their minimum inhibitory concentration (MIC) is 0.5 mcg/mL for trimethoprim and 9.5 mcg/mL for sulfonamide.^(R-25) However, the Clinical Laboratory and Standards Institute (CLSI; formerly NCCLS) in the U.S. lists MIC breakpoints for animal isolates and trimethoprim/sulfamethoxazole as ≤ 2 mcg per mL/38 mcg per mL for susceptible organisms and ≥ 4 mcg per mL/76 mcg per mL for resistant organisms.^(R-141) Organisms testing between these values are considered intermediate and may or may not be inhibited in certain body sites or with certain antimicrobials with low toxicity in which high concentrations can be achieved.^(R-141) These breakpoints are also used to test for susceptibility to sulfadiazine and trimethoprim or ormetoprim and sulfadimethoxine combination.^(R-141)

Sulfadiazine and trimethoprim—Calves:

1 day of age—A single intravenous dose of 25 mg of sulfadiazine and 5 mg of trimethoprim produced therapeutic serum concentrations > 2 mcg of sulfadiazine per mL of serum for 24 hours and > 0.1 mcg of trimethoprim per mL for 15 hours.^(R-79)

7 to 42 days of age—A single intravenous dose of 25 mg of sulfadiazine and 5 mg of trimethoprim produced therapeutic serum concentrations of > 2 mcg of sulfadiazine per mL of serum for 15 hours and > 0.1 mcg/mL of trimethoprim for 6 to 8 hours.^(R-79)

Sulfadoxine and trimethoprim—Cattle: Sulfadoxine serum concentrations exceeded 9.5 mcg/mL from 12 minutes to 10 hours postinjection and trimethoprim serum concentrations exceeded 0.5 mcg/mL from 15 minutes to 2 hours (intramuscular dose of 13.3 mg of sulfadoxine and 2.7 mg of

trimethoprim per kg of body weight) postinjection.^(R-85)

Elimination:

Sulfonamides—Renal excretion is the primary route of elimination for most nonenteric sulfonamides and it occurs by glomerular filtration of parent drug, tubular excretion of unchanged drug and metabolites, and passive reabsorption of nonionized drug.^(R-94; 110) Alkalinization of the urine increases the fraction of the dose that is eliminated in the urine.^(R-110) In general, the metabolites of the parent drug are more quickly eliminated by the kidney than is the original sulfonamide,^(R-75) but the proportions of metabolites formed can vary depending on many factors.

Sulfadimethoxine:

Cattle—Sulfadimethoxine is metabolized to a great degree, so that 40 to 60% of the administered dose is excreted as metabolites in the urine.^(R-111)

Dogs—Sulfadimethoxine is slowly excreted renally because of a high degree of tubular reabsorption.^(R-5)

Sulfadoxine: Horses—Sulfadoxine is excreted by glomerular filtration and reabsorption.^(R-34) The clearance of sulfadoxine increases with increasing pH.^(R-34)

Trimethoprim—Renal excretion occurs by glomerular filtration, active tubular secretion, and reabsorption.^(R-25; 89)

Dogs: Two-thirds of the total dose is eliminated in the urine as parent drug in the first 24 hours.^(R-19)

Horses: It is believed that a large percentage of trimethoprim is metabolized before elimination in urine (46%) and feces (52%).^(R-25; 26; 30) The clearance of trimethoprim is affected by urine pH, plasma concentration, and extent of diuresis,^(R-34) however, when sulfadiazine and trimethoprim are administered concurrently, neither antibiotic interferes with the excretion of the other.^(R-3; 4)

Total clearance—

Ormetoprim and sulfadimethoxine: Horses—

Ormetoprim: 11.1 mL per minute per kg (mL/min/kg).^(R-35)

Sulfadimethoxine: 0.42 mL/min/kg.^(R-35)

Sulfadiazine and trimethoprim:

Calves—

Sulfadiazine:

1 day of age—1.43 mL/min/kg.^(R-79)

1 week of age—1.7 mL/min/kg.^(R-79; 80)

6 weeks of age—1.88 mL/min/kg.^(R-79)

Trimethoprim:

1 day of age—2.8 mL/min/kg.^(R-79)

1 week of age—12 mL/min/kg.^(R-79; 80)

6 weeks of age—28.9 mL/min/kg.^(R-79)

Calves, ruminating—

Sulfadiazine: 3.15 mL/min/kg.^(R-77)

Trimethoprim: 6.6 mL/min/kg.^(R-77)

Horses—

Sulfadiazine: 1.92 mL/min/kg.^(R-43)

Trimethoprim: 8.49 mL/min/kg.^(R-43)

Pigs—

Sulfadiazine: 2.3 mL/min/kg.^(R-91)

Trimethoprim: 9.1 mL/min/kg.^(R-91)

Sulfamethoxazole and trimethoprim:

Horses—

Sulfamethoxazole: 1.3 mL/min/kg.^(R-31; 33)

Trimethoprim: 11.3 mL/min/kg.^(R-33) 14.8 mL/min/kg.^(R-31)

Horse foals—

Sulfamethoxazole: 0.83 mL/min/kg.^(R-32)

Trimethoprim: 17.1 mL/min/kg.^(R-32)

Pony foals—

Sulfamethoxazole: 1.1 mL/min/kg.^(R-32)

Trimethoprim: 11.7 mL/min/kg.^(R-32)

Sulfadimethoxine: Administered alone—

Cats: 0.32 mL/min/kg.^(R-102)

Dogs: 0.36 mL/min/kg.^(R-104)
Trout, rainbow: 0.36 mL/min/kg.^(R-70)

Precautions to Consider

Species sensitivity

Dogs: An idiosyncratic sulfonamide toxicosis can occur in any breed of dog, but the reaction has been reported more frequently in the Doberman Pinscher than in other breeds. This specific type of drug reaction includes blood dyscrasias, nonseptic polyarthritis, and skin rash.^(R-53; 54) See also the *Side Adverse Effects* section in this monograph.

Horses: Trimethoprim with sulfadiazine or trimethoprim with sulfadoxine infused into the uterus of horses can cause endometrial inflammation, straining, and expulsion of the medication. Conception rates may be lowered. Because there is good distribution of these medications when administered by systemic routes, intrauterine administration is not recommended.^(R-27)

Cross-sensitivity and/or related problems

Patients allergic to one sulfonamide may be allergic to other sulfonamides also.

Pregnancy/Reproduction

Sulfonamides and diaminopyrimidines cross the placenta in pregnant animals and some teratogenic effects have been seen with very high doses given to pregnant mice and rats.^(R-110)

Ormetoprim and sulfadimethoxine: **Dogs**—Safety in breeding or pregnant animals has not been established.^(R-5)

Pyrimethamine and sulfadiazine: **Horses**—Safety in breeding, pregnant, or lactating animals has not been evaluated.^(R-10)

Sulfadiazine and trimethoprim:

Dogs—The recommended dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight administered during pregnancy had no apparent effect on offspring.^(R-19)

Horses—Safety in pregnant animals has not been established.^(R-4) With administration of recommended doses, no changes in spermatogenesis in stallions were apparent.^(R-4)

Lactation

Sulfonamides are distributed into milk, with 0.5 to 2% of the total dose found in the milk.^(R-114; 115) For example, the milk-to-plasma concentration ratio for sulfadiazine and sulfadoxine was measured to be 0.5 in cows.^(R-75; 82)

Trimethoprim is distributed into milk.^(R-35) Trimethoprim concentrations in milk were found to be 1.3 to 3.5 times the plasma concentration measured at the same time in goats.^(R-73) The concentration of trimethoprim in the milk of cows is 1 to 3 times higher than in plasma and the concentration of trimethoprim in the milk of pigs is 1.3 to 3.5 times higher than in plasma.^(R-82; 83; 90)

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 the following medication, depending on the amount present, may also interact with this medication.
Detomidine

(a trimethoprim and sulfonamide combination administered to a detomidine-anesthetized horse can lead to arrhythmias, hypotension, and death; it is suspected that the antimicrobial potentiates the cardiac changes reported with detomidine)^(R-25; 120)

Human drug interactions^(R-96)

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 monographs *Sulfonamides (Systemic)* and

Trimethoprim (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 potentiated sulfonamides in the treatment of animals:

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

Anticoagulants, coumarin- or indandione-derivative, or
Anticonvulsants, hydantoin, or
Antidiabetic agents, oral

(these medications may be displaced from protein binding sites and/or their metabolism may be inhibited by some sulfonamides, resulting in increased or prolonged effects and/or toxicity; dosage adjustments may be necessary during and after sulfonamide therapy)

Bone marrow depressants

(concurrent use of bone marrow depressants with sulfonamides or aminopyrimidines may increase the leukopenic and/or thrombocytopenic effects; if concurrent use is required, close observation for myelotoxic effects should be considered)

Cyclosporine

(concurrent use with sulfonamides or trimethoprim may increase the metabolism of cyclosporine, resulting in decreased plasma concentrations and potential transplant rejection, and additive nephrotoxicity; plasma cyclosporine concentrations and renal function should be monitored)

Dapsone

(concurrent use with trimethoprim will usually increase the plasma concentrations of both dapsone and trimethoprim, possibly due to an inhibition in dapsone metabolism, and/or competition for renal secretion between the two medications; increased serum dapsone concentrations may increase the number and severity of side effects, especially methemoglobinemia)

Folate antagonists, other

(concurrent use with trimethoprim or use of trimethoprim between courses of other folic acid antagonists, such as pyrimethamine, is not recommended because of the possibility of an increased risk of megaloblastic anemia)

Hemolytics, other

(concurrent use with sulfonamides may increase the potential for toxic side effects)

Hepatotoxic medications, other

(concurrent use with sulfonamides may result in an increased incidence of hepatotoxicity; patients, especially those on prolonged administration or those with a history of liver disease, should be carefully monitored)

Methenamine

(in acid urine, methenamine breaks down into formaldehyde, which may form an insoluble precipitate with certain sulfonamides, especially those that are less soluble in urine, and may also increase the danger of crystalluria; concurrent use is not recommended)

Methotrexate or

Phenylbutazone or

Sulfinpyrazone

(the effects of methotrexate may be potentiated during concurrent use with sulfonamides because of displacement from plasma protein binding sites; phenylbutazone and sulfinpyrazone may displace sulfonamides from plasma protein binding sites, increasing sulfonamide concentrations)

Phenytoin

(trimethoprim may inhibit the hepatic metabolism of phenytoin, increasing the half-life of phenytoin by up to 50% and decreasing its clearance by 30%)

Procainamide

(concurrent use with trimethoprim may increase the plasma concentration of both procainamide and its metabolite NAPA by decreasing their renal clearance)

Rifampin

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

Warfarin

(trimethoprim may potentiate the anticoagulant activity of warfarin by inhibiting its metabolism)

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

Thyrotropin stimulation tests or

Total serum thyroxine (T₄)

(thyroid function tests may be lowered in dogs with administration of sulfamethoxazole and trimethoprim combination at high doses [25 mg of sulfamethoxazole and 5 mg of trimethoprim per kg of body weight every 12 hours for 6 weeks]^[R-62] or ormetoprim and sulfadimethoxine^[R-21] [8 weeks of medication with the labeled dose or with three to five times the labeled dose]; the T₄ and thyrotropin stimulation tests, but not T₃, may be significantly reduced;^[R-61] this effect was not shown with labeled doses of sulfadiazine and trimethoprim^[R-62])

With physiology/laboratory test values

Cholesterol, serum

(cholesterol concentrations can be elevated with administration of sulfonamides, including ormetoprim and sulfadimethoxine combination; however, this effect is reversible)^[R-5]

Human laboratory value alterations^[R-96]

In addition to the above laboratory value alterations reported in animals, the following laboratory value alterations have been reported in humans, and are included in the human monographs *Sulfonamides (Systemic)* and *Trimethoprim (Systemic)* in *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 potentiated sulfonamides in the treatment of animals:

With diagnostic test results

Benedict's test

(sulfonamides may produce a false-positive Benedict's test for urine glucose)

Creatinine determinations

(sulfamethoxazole or trimethoprim may interfere with the Jaffé alkaline picrate reaction assay for creatinine, resulting in creatinine values that are approximately 10% higher than actual values)

Sulfosalicylic acid test

(sulfonamides may produce a false-positive sulfosalicylic acid test for urine protein)

Urine urobilinogen test strip (e.g., Urobilistix)

(sulfonamides may interfere with the Urobilistix test for urinary urobilinogen)

With physiology/laboratory test values

Alanine aminotransferase (ALT [SGPT]), serum, and

Aspartate aminotransferase (AST [SGOT]), serum

(values may be increased)

Bilirubin, serum, and

Blood urea nitrogen (BUN) and

Creatinine, 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).

Except under special circumstances, this medication should not be used when the following medical problems exist:

» Blood dyscrasias^[R-25; 99]

(slight to moderate reduction in hematopoietic activity has been reported with long-term high dosing of potentiated sulfonamides)

» Hypersensitivity to diaminopyrimidines or sulfonamides^[R-5; 19]

(animals that have had a previous reaction may be much more likely to react on subsequent administration)

Risk-benefit should be considered when the following medical problems exist:

Hepatic function impairment^[R-5; 19; 25]

(delayed biotransformation may increase the risk of adverse effects)

Renal function impairment^[R-25]

(delayed elimination could cause accumulation of sulfonamide and metabolites, increasing the risk of adverse effects)

Urolithiasis^[R-25]

(sulfonamides can crystallize in the renal system under certain conditions)

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):

Complete blood count (CBC), including platelet count

(some animals have had reductions in hematopoietic activity when administered potentiated sulfonamides; periodic CBC and platelet counts are recommended if it is necessary to administer long-term treatment with potentiated sulfonamides)^[R-3; 19]

Culture and susceptibility, *in vitro*, and

Minimum inhibitory concentration (MIC)

(*in vitro* cultures and MIC test should be done on samples collected prior to potentiated sulfonamide administration to determine pathogen susceptibility)

Schirmer's tear test

(periodic Schirmer's tear tests during potentiated sulfonamide therapy in dogs may be warranted to monitor for early keratoconjunctivitis sicca)^[R-124]

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:

Those indicating need for medical attention

Incidence more frequent

Horses

Blood dyscrasias, including generalized bone marrow suppression, anemia, leukopenia, neutropenia, or

thrombocytopenia—with pyrimethamine and sulfadiazine in the treatment of equine protozoal myeloencephalitis (EPM)^[R-10]

Note: When 37 horses were administered 1 mg of pyrimethamine and 20 mg of sulfadiazine per kg a day for at least 90 days in a field trial, 22%, 19%, 5% and 3% developed anemia, leukopenia, neutropenia, and thrombocytopenia, respectively. Incidence and severity of bone marrow suppression were dose-related. The effects resolved with interruption in treatment.

Incidence unknown

For all species

Crystallization in the urinary tract;^[R-5] **hypersensitivity, specifically anaphylaxis**^[R-4; 5]

Note: *Crystallization* of sulfonamides is theoretically possible with administration of potentiated sulfonamides; however, the lower doses of sulfonamide used in the potentiated sulfonamide combination makes crystallization less likely to occur than with sulfonamide administered alone. Sulfonamides can crystallize in the kidneys or urine in animals with aciduria, with high doses of sulfonamide, or with dehydration. The amount of drug in the acetylated metabolite form also can affect solubility. Because dogs do not produce acetylated metabolites, they may be less susceptible to this adverse effect.^[R-123] Crystallization also can be minimized in susceptible animals by maintaining a high urine flow and, if necessary, alkalinizing the urine.

Dogs

Anemia, hemolytic;^[R-5; 19] **anemia, nonregenerative;**^[R-23; 51] **anorexia;**^[R-5; 19] **cutaneous drug eruption, including erythema multiforme, perforating folliculitis, and pustular dermatitides;**^[R-54; 60] **diarrhea;**^[R-5; 19] **facial swelling;**^[R-5; 19] **fever;**^[R-5; 19] **hepatitis;**^[R-5; 19; 52; 54] **hypothyroidism;**^[R-21; 61; 62] **idiosyncratic toxicosis** (blood dyscrasias, including anemia, leukopenia, or thrombocytopenia; fever; focal retinitis; lymphadenopathy; nonseptic polyarthritis; polymyositis; skin rash);^[R-53; 54; 57-60] **keratoconjunctivitis sicca;**^[R-5; 19; 55; 56] **neurologic disorders** (aggression, ataxia, behavioral changes, hyperexcitability, seizures);^[R-19] **polyarthritis;**^[R-5; 19] **polydipsia/polyuria;**^[R-5; 19] **thrombocytopenia**—one case reported without other blood lines affected;^[R-116] **urticaria;**^[R-5; 19] **vomiting**^[R-5; 19]

Note: *Idiosyncratic toxicosis* can occur 8 to 20 days after starting treatment and is believed to be caused by either an immune-mediated syndrome or by an idiosyncratic reaction in dogs, perhaps due to toxic metabolites of the sulfonamide. Of 22 reported cases compiled in one study, 7 were Doberman Pinschers and it has been theorized that they are more susceptible than other breeds to this toxicosis.^[R-53; 54] A large majority of the animals in which idiosyncratic toxicosis occurs have had a previous exposure to a sulfonamide.^[R-54] When sulfonamide therapy is discontinued, recovery generally occurs within 2 to 5 days.^[R-54; 60]

Keratoconjunctivitis sicca is considered a possible side/adverse effect in any dog administered sulfonamides; it can occur at any time after therapy is initiated. The most frequent reports have been with sulfasalazine or trimethoprim and sulfonamide combination,^[R-55; 56] perhaps because these medications are most commonly used for long-term therapy in dogs. As many as 15% (5 out of 33 in one study) of dogs treated with sulfadiazine and trimethoprim may develop keratoconjunctivitis sicca.^[R-124] While increased risk has not been linked to higher dose or longer treatment, dogs weighing less than 12 kg may be at increased risk.^[R-124] Lacrimation may return to normal after discontinuation of sulfonamide treatment.

The *nonregenerative anemias* seen in response to long-term administration of sulfadiazine and trimethoprim combination are, in some cases, believed to be related to folate reduction with long-term, high-dose administration (60 to 120 mg/kg a day for many weeks) of potentiated sulfonamide;^[R-23; 50] these anemias generally respond well to withdrawal of the medication.^[R-23] In the event an animal does not respond to medication withdrawal, folic or folic acid supplementation may be necessary.^[R-137; 138]

Iatrogenic *hypothyroidism* may occur and thyroid function test results may be lowered with administration of sulfamethoxazole and trimethoprim combination at high doses (25 mg of sulfamethoxazole and 5 mg of trimethoprim per kg every 12 hours for 6 weeks)^[R-62] or ormetoprim and sulfadimethoxine^[R-21] (8-week medication with the labeled dose or with three to five times the labeled dose). Results of the T₄ and thyrotropin stimulation tests, but not T₃, may show significant reduction;^[R-61] this effect was not shown

with labeled doses of sulfadiazine and trimethoprim (12.5 mg of sulfadiazine and 2.5 mg of trimethoprim per kg every 12 hours for 4 weeks).^[R-62]

Horses

Diarrhea—reported in horses treated with either pyrimethamine or trimethoprim with a sulfonamide;^[R-3; 10; 139] **hypersensitivity reactions** (anorexia; decreased hematopoiesis;^[R-3] loose stool; or muscle tremors)—with intravenous administration of potentiated sulfonamides;^[R-25; 26; 35] **urticaria**—reported with pyrimethamine and sulfadiazine; cases resolved without treatment;^[R-10] **worsening of neurologic deficits**—with pyrimethamine and sulfadiazine in the treatment of equine protozoal myeloencephalitis^[R-10]

Pigs

Thyroid hyperplasia—in gilts, sows and piglets; believed to be in response to the sulfadimethoxine component of ormetoprim and sulfadimethoxine combination^[R-92]

For sulfaquinoxaline

Chickens and dogs

Hemorrhagic syndrome (anorexia, epistaxis, hemoptysis, lethargy, pale mucous membranes, death)^[R-100; 112; 113; 121; 122]

Note: *Hemorrhagic syndrome* has been reported in chickens and dogs but may occur in other species. It is most often reported with the addition of sulfaquinoxaline to feed for chickens, but in dogs, reports follow administration of products labeled for poultry but administered to dogs in the water supply.^[R-112; 113; 121; 122] Sulfaquinoxaline is a vitamin K antagonist that inhibits vitamin K epoxide and vitamin K quinone reductase and causes an effect similar to that of coumarin anticoagulants.^[R-100] Rapid hypoprothrombinemia occurs in dogs and an additional adverse effect of sulfaquinoxaline on specific cell types may explain why supplementation of chicken feeds with vitamin K has not always prevented the syndrome in chickens.^[R-100; 112] Rapid discontinuation of medication and initiation of therapy with vitamin K₁ may reverse the effects.

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Cattle or horses

Local pain and swelling—with intramuscular injection of sulfonamide and trimethoprim^[R-9; 13; 14]

Pigs

Irritant reactions—with intramuscular injection;^[R-14] **vomiting**—with oral suspension of sulfadiazine and trimethoprim combination^[R-10]

Human side/adverse effects^[R-96]

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 monographs *Sulfonamides (Systemic)* and *Trimethoprim (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 potentiated sulfonamides in the treatment of animals:

For sulfonamides—

Incidence more frequent

Central nervous system (CNS) effects; gastrointestinal disturbances; hypersensitivity; photosensitivity

Incidence less frequent

Blood dyscrasias; hepatitis; Lyell's syndrome (difficulty in swallowing; redness, blistering, peeling, or loosening of skin); **Stevens-Johnson syndrome** (aching joints and muscles; redness, blistering, peeling, or loosening of skin; unusual tiredness or weakness)

Incidence rare

CNS toxicity; Clostridium difficile colitis; crystalluria or hematuria; goiter or thyroid function disturbance; interstitial nephritis or tubular necrosis

Note: Fatalities have occurred, although rarely, due to severe

reactions such as *Stevens-Johnson syndrome*, fulminant *hepatic necrosis*, agranulocytosis, aplastic anemia, and other *blood dyscrasias*. Therapy should be discontinued at the first appearance of skin rash or any serious side/adverse effects. *Crystalluria* is more likely to occur with a less soluble sulfonamide, such as sulfadiazine. It occurs most often with the administration of high doses, and can be minimized by maintaining a high urine flow and alkalizing the urine. *C. difficile colitis* may occur up to several weeks after discontinuation of these medications.

For trimethoprim—

Incidence less frequent

Gastrointestinal disturbances; headache; pruritis; skin rash

Incidence rare

Anaphylaxis; aseptic meningitis; blood dyscrasias, such as leukopenia or neutropenia, megaloblastic anemia, and thrombocytopenia; glossitis; methemoglobinemia; phototoxicity; severe skin reactions, such as erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis [Lyell's syndrome]

Overdose

For more information in cases 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 drug manufacturer.**

Acute toxicities appear to be difficult to induce; those reported below are in response to a dose five times the loading dose and ten times the maintenance dose on the product label.

Clinical effects of overdose

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

For ormetoprim and sulfadimethoxine^(R-21)

Dogs (53 mg ormetoprim and 267 mg sulfadimethoxine per kg of body weight dose or 160 mg ormetoprim per kg administered alone)

Convulsions; hyperglycemia, mild

Treatment of overdose

Recommended treatment consists of the following:

- Discontinuing medication.
- Administering intravenous diazepam or other acute antiseizure medication, as needed.
- Providing fluid replacement therapy as required.

Client Consultation

Dosage and length of treatment recommendations should be followed.

High doses or long-term use can increase the risk of side effects.

Animals should have a good water supply and should be monitored to insure their adequate water consumption during treatment.^(R-3)

General Dosing Information

Although the minimum inhibitory concentrations (MICs) of potentiated sulfonamides are important in determining therapeutic regimens, they can be misleading because the actual concentrations of drugs at the therapeutic site can be difficult to pinpoint at any one time. Trimethoprim goes rapidly into tissues, and sulfonamides often have measurable serum concentrations for longer periods. The ratio of sulfonamide to trimethoprim concentrations necessary at the site for efficacy may vary from the goal of 20 to 1, depending on the tissue and the local concentrations of other factors, such as thymidine.^(R-24) Clinical efficacy also should be considered, once pathogen susceptibility has been determined.^(R-24; 31)

The Clinical Laboratory and Standards Institute (CLSI; formerly

NCCLS) in the U.S. lists MIC breakpoints for animal isolates and trimethoprim/sulfamethoxazole as ≤ 2 mcg per mL/38 mcg per mL for susceptible organisms and ≥ 4 mcg per mL/76 mcg per mL for resistant organisms.^(R-141) Organisms testing between these values are considered intermediate and may or may not be inhibited in certain body sites in which high concentrations can be achieved or with certain antimicrobial agents with low toxicity.^(R-141) These breakpoints are also used to test for susceptibility to sulfadiazine and trimethoprim or ormetoprim and sulfadimethoxine combination.^(R-141)

For oral dosage forms only

Horses: Some horses will develop diarrhea when administered potentiated sulfonamides.^(R-3; 10) However, the oral administration of 25 to 100 mg of sulfadiazine and 5 to 20 mg of trimethoprim per kg of body weight a day for 5 days does not cause the increase in coliform bacteria and *Clostridium perfringens* type A associated with induced colitis. At the highest dose, a slight decrease in coliform count is noted in healthy horses.^(R-40) Having free access to feed does not significantly affect the horse's ability to absorb sulfadiazine during administration of oral sulfadiazine and trimethoprim combination. The absorption of trimethoprim is delayed so initial serum concentrations will be lower in a fed horse than in a fasted horse; however, this effect is greatly decreased by the third day of treatment.^(R-27)

For treatment of adverse effects

Recommended treatment consists of the following:

For anaphylaxis

- Parenteral epinephrine.
- Oxygen administration and respiratory support.

ORMETOPRIM AND SULFADIMETHOXINE

Oral Dosage Forms

Note: The text between ^{ELUS} and ^{EL} describes uses not included in U.S. product labeling. Text between ^{ELCAN} and ^{EL} describes uses that are not included in Canadian product labeling.

The ^{ELUS} or ^{ELCAN} designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

ORMETOPRIM AND SULFADIMETHOXINE TYPE A MEDICATED ARTICLE

Usual dose:

^{ELCAN} Coccidiosis (prophylaxis)^{EL}—

Chickens and partridges, chukar: Oral, 68.1 grams of ormetoprim and 113.5 grams of sulfadimethoxine per ton of feed, fed as the only ration.^(R-6; 125)

Turkeys: Oral, 34 grams of ormetoprim and 56.8 grams of sulfadimethoxine per ton of feed, fed as the only ration.^(R-6)

Withdrawal times—*Chickens and turkeys:* US—Meat: 5 days.^(R-6; 7) Product labeling states that this combination is not for use in birds producing eggs for human consumption or for chickens over 16 weeks of age.^(R-6) *Partridges:* US—Products are labeled for use in young birds up to eight weeks of age.^(R-6)

^{ELCAN} Colibacillosis (prophylaxis)^{EL}—*Chickens:* Oral, 68.1 grams of ormetoprim and 113.5 grams of sulfadimethoxine per ton of feed, fed as the only ration.^(R-6)

Withdrawal times—US: Meat—5 days.^(R-6; 7) Product labeling states that this combination is not for use in birds producing eggs for food or for chickens over 16 weeks of age.^(R-6)

^{ELCAN} Colibacillosis (treatment)^{EL}—*Ducks:* Oral, 272.4 grams of ormetoprim and 454 grams of sulfadimethoxine per ton of feed, fed as the only ration for seven days.^(R-6)

Withdrawal times—US: Meat—5 days.^(R-6;7) Product labeling states that this combination is not for use in birds producing eggs for human consumption.^(R-6)

^{ELCAN}Enteric septicemia^{EL}—*Catfish*: Oral, 8 mg of ormetoprim and 42 mg of sulfadimethoxine per kg of body weight a day, administered in the feed and fed as the only ration for five days.^(R-7; 16)

Withdrawal times—US: Meat—3 days.^(R-7; 16)

^{ELCAN}Fowl cholera (prophylaxis)^{EL}—

Chickens: Oral, 68.1 grams of ormetoprim and 113.5 grams of sulfadimethoxine per ton of feed, fed as the only ration.^(R-6)

Turkeys: Oral, 34 grams of ormetoprim and 56.8 grams of sulfadimethoxine per ton of feed, fed as the only ration.^(R-6)

Withdrawal times—US: Meat—5 days.^(R-6;7) Product labeling states that this combination is not for use in birds producing eggs for human consumption or for chickens over 16 weeks of age.^(R-6)

^{ELCAN}Fowl cholera (treatment)^{EL}—*Ducks*:

Routine—Oral, 136.2 grams of ormetoprim and 227 grams of sulfadimethoxine per ton of feed, fed as the only ration for seven days.^(R-6)

Severe—Oral, 272.4 grams of ormetoprim and 454 grams of sulfadimethoxine per ton of feed, fed as the only ration for seven days.^(R-6)

Withdrawal times—US: Meat—5 days.^(R-6;7) Product labeling states that this combination is not for use in birds producing eggs for human consumption.^(R-6)

Furunculosis—*Salmon and trout*: Oral, 8 mg of ormetoprim and 42 mg of sulfadimethoxine per kg of body weight a day, administered in the feed, and fed as the only ration for five days.^(R-7; 16)

Withdrawal times—US and Canada: Meat—42 days.^(R-7; 16)

Canadian product labeling states that this withdrawal time applies to a dose of 15 mg per kg of body weight a day when the water temperature is ≥ 10 °C.

^{ELCAN}Infectious coryza (prophylaxis)^{EL}—*Chickens*: Oral, 68.1 grams of ormetoprim and 113.5 grams of sulfadimethoxine per ton of feed, fed as the only ration.^(R-6)

Withdrawal times—US: Meat—5 days.^(R-6;7) Product labeling states that this combination is not for use in birds producing eggs for human consumption or for chickens over 16 weeks of age.^(R-6)

^{ELCAN}New duck disease^{EL}—*Ducks*: Oral, 272.4 grams of ormetoprim and 454 grams of sulfadimethoxine per ton of feed, fed as the only ration for seven days.^(R-6)

Withdrawal times—US: Meat—5 days.^(R-6;7) Product labeling states that this combination is not for use in birds producing eggs for human consumption.^(R-6)

Strength(s) usually available:^(R-95)

U.S.—

Veterinary-labeled product(s):

50 grams of ormetoprim and 250 grams of sulfadimethoxine per kg of premix (OTC) [*Romet 30* (catfish and salmonids)].

150 grams of ormetoprim and 250 grams of sulfadimethoxine per kg of premix (OTC) [*Rofenaid 40* (chickens, ducks, partridges, and turkeys)].

Canada—

Veterinary-labeled product(s):

50 grams of ormetoprim and 250 grams of sulfadimethoxine per kg of premix (Rx) [*Romet-30* (salmonids)].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer.

Additional information: Canadian labeling states that the product should not be used when the water temperature is below 10 °C.^(R-16)

USP requirements: Not in USP.

ORMETOPRIM AND SULFADIMETHOXINE TABLETS

Usual dose:

^{ELCAN}Skin and soft tissue infections^{EL}; or

^{ELCAN}Urinary tract infections^{EL}—*Dogs*: Oral, 9.2 mg of ormetoprim and 45.8 mg of sulfadimethoxine per kg of body weight as an initial dose, followed by 4.6 mg of ormetoprim and 22.9 mg of trimethoprim per kg of body weight every twenty-four hours.^(R-5) Administration for more than twenty-one days is not recommended.^(R-5)

Note: ^{ELUS,CAN}Enteric coccidiosis—*Dogs*: Although the efficacy has not been established, a dose of 11 mg of ormetoprim and 55 mg of sulfadimethoxine a day has been used in the treatment of *enteric coccidiosis* in dogs. This therapy may reduce shedding of oocysts and relieve symptoms.^{EL(R-136)}

Strength(s) usually available:

U.S.—^(R-5)

Veterinary-labeled product(s):

20 mg of ormetoprim and 100 mg of sulfadimethoxine (Rx) [*Primor 120*].

40 mg of ormetoprim and 200 mg of sulfadimethoxine (Rx) [*Primor 240*].

100 mg of ormetoprim and 500 mg of sulfadimethoxine (Rx) [*Primor 600*].

200 mg of ormetoprim and 1000 mg of sulfadimethoxine (Rx) [*Primor 1200*].

Canada—

Veterinary-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), unless otherwise specified by the manufacturer.

USP requirements: Not in USP.

PYRIMETHAMINE AND SULFADIAZINE

Oral Dosage Forms

Note: The text between ^{ELUS} and ^{EL} describes uses not included in U.S. product labeling. Text between ^{ELCAN} and ^{EL} describes uses that are not included in Canadian product labeling.

The ^{ELUS} or ^{ELCAN} designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

PYRIMETHAMINE AND SULFADIAZINE ORAL SOLUTION

Usual dose: ^{ELCAN}Equine protozoal myeloencephalitis (treatment)^{EL}—

Horses: Oral, 1 mg of pyrimethamine and 20 mg of sulfadiazine per kg of body weight every twenty-four hours, administered at least one hour before feeding hay or grain.^(R-10) Treatment is typically administered for ninety to two hundred and seventy days, depending on clinical response.^(R-10)

Withdrawal times—This product is not labeled for use in horses intended for human consumption.^(R-10)

Strength(s) usually available:

U.S.—

Veterinary-labeled product(s):

12.5 mg of pyrimethamine and 250 mg of sulfadiazine per mL of suspension (Rx) [*Rebalance*].
Canada—
Veterinary-labeled product(s):
Not commercially available.

Packaging and storage: Store between 15 and 30 °C (59 to 86 °F), unless otherwise specified by the manufacturer. Protect from freezing.^(R-10)

Auxiliary labeling: Shake well before using.^(R-10)

USP requirements: Not in USP.

PRIMETHAMINE AND SULFAQUINOXALINE

Oral Dosage Forms

Note: The text between ^{ELUS} and ^{EL} describes uses not included in U.S. product labeling. Text between ^{ELCAN} and ^{EL} describes uses that are not included in Canadian product labeling.

The ^{ELUS} or ^{ELCAN} designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

PRIMETHAMINE AND SULFAQUINOXALINE ORAL SOLUTION

Usual dose: ^{ELUS}Coccidiosis (prophylaxis and treatment)^{EL}—*Chickens and turkeys:* Oral, 14.7 mg of pyrimethamine and 48.8 mg of sulfaquinoxaline per liter of water, administered as the only source of drinking water for two days. Treatment is stopped for three days and then repeated as necessary to control infection. For existing infection, treatment should be repeated until symptoms of disease have disappeared.^(R-17)

Withdrawal times—Canada: Meat—4 days.^(R-17)

Strength(s) usually available:^(R-95)

U.S.—

Veterinary-labeled product(s):
Not commercially available.

Canada—^(R-17)

Veterinary-labeled product(s):
9.8 grams of pyrimethamine and 32.5 grams of sulfaquinoxaline per liter of solution (OTC) [*Quimoxine-S; Sulfaquinoxaline-S*].

Packaging and storage: Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer. Protect from light.^(R-17)

USP requirements: Not in USP.

SULFADIAZINE AND TRIMETHOPRIM

Oral Dosage Forms

Note: The text between ^{ELUS} and ^{EL} describes uses not included in U.S. product labeling. Text between ^{ELCAN} and ^{EL} describes uses that are not included in Canadian product labeling.

The ^{ELUS} or ^{ELCAN} designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

SULFADIAZINE AND TRIMETHOPRIM ORAL PASTE

Usual dose:

^{ELCAN}Respiratory tract infections^{EL};
^{ELCAN}Skin and soft tissue infections^{EL};

^{ELCAN}Strangles^{EL}; or
^{ELCAN}Urogenital infections^{EL}

—*Horses:* Oral, 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight every twenty-four hours.^(R-3)

Withdrawal times—US: Sulfadiazine and trimethoprim oral paste is not labeled for use in food-producing animals, including horses intended for food production.

Note: ^{ELUS,CAN}Infections, bacterial, including equine infectious arthritis—*Horses:* Based on pharmacokinetic studies, disease models of infectious arthritis, and the relatively short half-life of trimethoprim in the horse, an oral dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight every twelve hours has been used to treat susceptible infections in horses.^(R-25) For equine infectious arthritis, the dose is administered for three to six weeks.^(R-41; 42)

The administration of oral sulfadiazine and trimethoprim combination while a horse has free access to feed does not significantly affect the absorption of the sulfadiazine.^(R-25; 27; 28) however, the absorption of trimethoprim is delayed so that initial serum concentrations will be lower in a fed horse than in a fasted horse. This effect is greatly decreased by the third day of treatment.^(R-27) For horses being treated for less severe, susceptible infections, allowing free access to food is recommended to decrease the risk of diarrhea.^{EL(R-25)}

^{ELUS,CAN}Pneumonia, bacterial—*Calves,* prerinuating: At one time, Canadian sulfadiazine and trimethoprim boluses were labeled for use in the treatment of bacterial pneumonia in calves.^(R-12) Although there are no products labeled for use in calves in the United States or Canada at this time, oral sulfadiazine and trimethoprim might be used in the treatment of susceptible infections in calves.^{EL}

In ruminating calves, therapeutic serum concentrations of trimethoprim have not been reached with oral administration.^(R-12; 81) Increased rate of elimination and decreased absorption of the medication as calves mature lead to a decrease in resulting serum antibiotic concentration that is measurable at 6 weeks of age in milk-fed calves and becomes so pronounced with onset of rumination that this medication cannot be administered effectively.^(R-79; 81; 143)

According to some researchers, many pathogens important in calfhood diseases, including *Escherichia coli*, *Salmonella* species, and *Haemophilus* species, have minimum inhibitory concentrations (MICs) that range from 3 to 10 mcg per mL (mcg/mL) for sulfonamides and 0.1 to 0.5 mcg/mL for trimethoprim.^(R-24; 81; 143) Researchers have suggested that, in calves less than 1 week of age, oral administration of 12.5 mg of sulfadiazine and 2.5 mg of trimethoprim per kg of body weight every 24 hours would be appropriate in the treatment of infections caused by these organisms.^(R-81) They note that in animals older than 1 week of age, an oral dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight, administered every 12 hours, has been necessary to maintain therapeutic concentrations.^(R-81) However, the Clinical Laboratory and Standards Institute (CLSI; formerly NCCLS) lists MIC breakpoints for animal isolates and trimethoprim/sulfonamide as ≤ 2 mcg per mL/38 mcg per mL, respectively, for susceptible organisms and ≥ 4 mcg per mL/76 mcg per mL for resistant organisms.^(R-141) It is possible for an organism to be classified as sensitive yet have MICs above the plasma concentration achieved by the above dosages.^(R-145) Based on pharmacokinetic calculations, an oral dosage of 37.5 mg of sulfadiazine and 7.5 mg of trimethoprim per kg of body weight every 12 hours in calves older than 1 week of age but younger than 6 weeks of age may be needed to consistently maintain concentrations greater than or equal to the CLSI breakpoints, but the safety and efficacy of such a dose has not been tested in calves.^(R-144; 145)

Extra-label withdrawal times—It should be considered that

substitution of one oral dosage form for another may result in different in pharmacokinetic results. Available residue studies and pharmacokinetic studies for oral products were performed in calves using boluses and tablets, respectively.^(R-81; 140)

U.S.: Sulfadiazine and trimethoprim products are not labeled for use in food-producing animals in the U.S.; therefore, there is no established withdrawal time for calves.

If an oral sulfadiazine and trimethoprim combination product available in the U.S. is administered to 1-week-old calves at a dose of 12.5 mg of sulfadiazine and 2.5 mg of trimethoprim every twelve hours, the Food Animal Residue Avoidance Databank (FARAD) notes that there is some evidence to suggest a meat withdrawal time of 12 days would be sufficient to avoid violative residues in the U.S.^(R-12; 79; 80; 81; 140; 142) Estimates for a withdrawal time for dosages larger than 12.5 mg of sulfadiazine and 2.5 mg of trimethoprim every twelve hours are not available.

Canada: Because there is no sulfadiazine and trimethoprim product labeled for use in calves in Canada, there is no established withdrawal time. If an oral sulfadiazine and trimethoprim combination product is administered to 1-week-old calves at a dose of 12.5 mg of sulfadiazine and 2.5 mg of trimethoprim every twelve hours, there is some evidence to suggest that a meat withdrawal time of 10 days, the discontinued Canadian product label withdrawal time, would be sufficient to avoid residues that would violate U.S. standards.^(R-12; 79; 80; 81; 140; 142) Estimates for a withdrawal time for dosages larger than 12.5 mg of sulfadiazine and 2.5 mg of trimethoprim every twelve hours are not available.

Strength(s) usually available:^(R-95)

U.S.—^(R-3)

Veterinary-labeled product(s):
333 mg of sulfadiazine and 67 mg of trimethoprim per gram of paste (Rx) [*Tribriksen 400 Oral Paste*].

Canada—

Veterinary-labeled product(s):
Not commercially available.

Packaging and storage: Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer.^(R-3)

USP requirements: Not in USP.

SULFADIAZINE AND TRIMETHOPRIM ORAL POWDER

Usual dose:

Respiratory tract infections;
Skin and soft tissue infections;
Strangles; or
^{EL,CAN}Urogenital infections^{EL}—*Horses*: Oral, 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight every twenty-four hours.^(R-4; 11; 126)
Withdrawal times—US: Sulfadiazine and trimethoprim oral powder is not labeled for use in food-producing animals, including horses intended for food production.^(R-4; 11; 126)
Canada: Meat—7 days.^(R-11)

Note: ^{EL,US,CAN}Based on pharmacokinetic studies, an oral dose of 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight every twelve hours has also been used in horses.^(R-25)

The administration of oral sulfadiazine and trimethoprim combination while a horse has free access to feed does not significantly affect the absorption of the sulfadiazine;^(R-25; 27; 28) however, the absorption of trimethoprim is delayed so initial serum concentrations will be lower in a fed horse than in a fasted horse. This effect is greatly decreased by the third day of treatment.^(R-27) For horses being treated for less severe, susceptible infections, allowing free access to food is

recommended to decrease the risk of diarrhea.^(R-25)

^{EL,US}*Vibrio anguillarum* infection^{EL}—*Salmon*: Oral, 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight a day, administered in the feed, and fed as the only ration for seven to ten days.^(R-22)

Withdrawal times—Canada: Meat—80 days.^(R-22) The half-lives of sulfadiazine and trimethoprim in the deepest layer of marine sediments can be ninety days or longer.^(R-65)

Note: ^{EL,US,CAN}Pneumonia, bacterial—*Calves*, preruminating: See *Sulfadiazine and Trimethoprim Oral Paste*, above in this monograph.^{EL}

Strength(s) usually available:

U.S.—^(R-126)

Veterinary-labeled product(s):
333 mg of sulfadiazine and 67 mg of trimethoprim per gram of powder (Rx) [*Tucoprim; Uniprim*].

Canada—^(R-11; 22)

Veterinary-labeled product(s):
333 mg of sulfadiazine and 67 mg of trimethoprim per gram of powder (Rx) [*Tribriksen 40% Powder* (salmon); *Uniprim* (horses)].

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.^(R-22)

USP requirements: Not in USP.

Parenteral Dosage Forms

Note: The text between ^{EL,US} and ^{EL} describes uses not included in U.S. product labeling. Text between ^{EL,CAN} and ^{EL} describes uses that are not included in Canadian product labeling.

The ^{EL,US} or ^{EL,CAN} designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

SULFADIAZINE AND TRIMETHOPRIM INJECTION

Usual dose:

^{EL,US}Gastrointestinal tract infections^{EL}—*Cats and dogs*:
Subcutaneous, 12.5 mg of sulfadiazine and 2.5 mg of trimethoprim per kg of body weight every twelve hours or, less commonly, 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight every twenty-four hours.^(R-8)

^{EL,US}Postoperative infections^{EL}; or

^{EL,US}Strangles^{EL}—*Horses*: Intramuscular or intravenous, 20 mg of sulfadiazine and 4 mg of trimethoprim per kg of body weight every twenty-four hours.^(R-9)

Withdrawal times—Canada: Sulfadiazine and trimethoprim injection is not labeled for use in horses intended for human consumption.^(R-9)

^{EL,US}Respiratory tract infections^{EL}; or

^{EL,US}Skin and soft tissue infections^{EL}—

Cats and dogs: Subcutaneous, 12.5 mg of sulfadiazine and 2.5 mg of trimethoprim per kg of body weight every twelve hours or, less commonly, 25 mg of sulfadiazine and 5 mg of trimethoprim per kg of body weight every twenty-four hours.^(R-8)

Horses: Intramuscular or intravenous, 20 mg of sulfadiazine and 4 mg of trimethoprim per kg of body weight every twenty-four hours.^(R-9)

Withdrawal times—Canada: Sulfadiazine and trimethoprim injection is not labeled for use in horses intended for human consumption.^(R-9)

Note: Although Canadian labeling recommends intramuscular or intravenous administration of sulfadiazine and trimethoprim

combination and there are few reports in the literature of adverse reactions to intravenous administration of this combination, some sources recommend caution when administering these medications intravenously to horses.^[R-25]

Product labeling states that administration for more than seven days in horses is not recommended.^[R-8; 9]

Note: ^{ELUS,CAN} Meningitis, bacterial—*Dogs*: Although the safety and efficacy have not been established, if a sulfonamide with trimethoprim is administered in the treatment of bacterial meningitis in dogs, a dose of 25 mg of sulfonamide and 5 mg of trimethoprim every twelve hours has been suggested. Patients should be monitored for potential adverse effects associated with high doses of potentiated sulfonamides.

Strength(s) usually available:^[R-95]

U.S.—

Veterinary-labeled product(s):
Not commercially available.

Canada—

Veterinary-labeled product(s):
200 mg of sulfadiazine and 40 mg of trimethoprim per mL (Rx) [*Tribriksen 24%* (cats and dogs)].
400 mg of sulfadiazine and 80 mg of trimethoprim per mL (Rx) [*Tribriksen 48%* (horses)].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer.

USP requirements: Not in USP.

SULFADOXINE AND TRIMETHOPRIM

Parenteral Dosage Forms

Note: The text between ^{ELUS} and ^{EL} describes uses not included in U.S. product labeling. Text between ^{ELCAN} and ^{EL} describes uses that are not included in Canadian product labeling.

The ^{ELUS} or ^{ELCAN} designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

SULFADOXINE AND TRIMETHOPRIM INJECTION

Usual dose:

^{ELUS} Bacterial enteritis^{EL};

^{ELUS} Bacterial pneumonia^{EL}; or

^{ELUS} Colibacillosis^{EL}—*Cattle and pigs*: Intramuscular or slow intravenous, 13.3 mg of sulfadoxime and 2.7 mg of trimethoprim per kg of body weight, every twenty-four hours for five days.^[R-13-15]

Withdrawal times—Canada: *Cattle*—Meat: 10 days, Milk: 96 hours. *Pigs*—Meat 10 days.^[R-13-15]

Note: ^{ELUS} *Cattle*—^{ELCAN} Based on pharmacokinetic studies, a dose of 13.3 mg of sulfadoxime and 2.7 mg of trimethoprim per kg of body weight every twelve hours may be necessary to treat infections in cattle caused by organisms that are less than very sensitive to sulfadoxime and trimethoprim.^{EL}^[R-85]

^{ELUS} Bacterial arthritis^{EL};

^{ELUS} Mastitis^{EL}; or

^{ELUS} Metritis^{EL}—*Pigs*: Intramuscular or slow intravenous, 13.3 mg of sulfadoxime and 2.7 mg of trimethoprim per kg of body weight every twenty-four hours for five days.^[R-13-15]

Withdrawal times—Canada: Meat—10 days.^[R-13-15]

^{ELUS} Pododermatitis^{EL}; or

^{ELUS} Septicemia^{EL}—*Cattle*: Intramuscular or slow intravenous, 13.3 mg of sulfadoxime and 2.7 mg of trimethoprim per kg of body

weight, every twenty-four hours for five days.^[R-13-15]

Withdrawal times—Canada: Meat—10 days, Milk—96 hours.^[R-13-15]

Strength(s) usually available:^[R-95]

U.S.—

Veterinary-labeled product(s):
Not commercially available.

Canada—

Veterinary-labeled product(s):
200 mg of sulfadoxime and 40 mg of trimethoprim per mL (Rx) [*Borgal*; *Novovet TMPS*; *Potensulf*; *Trimidox*; *Trivetrin*].

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

USP requirements: Not in USP.

SULFAMETHOXAZOLE AND TRIMETHOPRIM

Oral Dosage Forms

Note: The text between ^{ELUS} and ^{EL} describes uses not included in U.S. product labeling. Text between ^{ELCAN} and ^{EL} describes uses that are not included in Canadian product labeling.

The ^{ELUS} or ^{ELCAN} designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

SULFAMETHOXAZOLE AND TRIMETHOPRIM ORAL SUSPENSION USP

Usual dose:

Note: ^{ELUS,CAN} Prostatitis, bacterial—*Dogs*: Although the safety and efficacy have not been established, an oral dose of 25 mg of sulfamethoxazole and 5 mg of trimethoprim per kg of body weight every twelve hours for two to four weeks has been used, based on pharmacokinetic data.^{EL}^[R-47; 48]

^{ELUS,CAN} Infections, bacterial—*Horses*: Although the safety and efficacy have not been established, an oral dose of 25 mg of sulfamethoxazole and 5 mg of trimethoprim per kg of body weight every twelve hours has been used, based on pharmacokinetic studies.^{EL}^[R-31]

Strength(s) usually available:

U.S.—^[R-119]

Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
40 mg of sulfamethoxazole and 8 mg of trimethoprim per mL (Rx) [*Septra Grape Suspension*; *Septra Suspension* (cherry flavored); *Sulfatrim Suspension*; GENERIC].

Canada—

Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
40 mg of sulfamethoxazole and 8 mg of trimethoprim per mL (Rx) [*Apo-Sulfatrim*; *Novo-Trimef*].

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

USP requirements: Preserve in tight, light-resistant containers. Contains the labeled amounts, within ±10%. Meets the

requirements for Identification, pH (5.0–6.5), Chromatographic purity, and Alcohol content (not more than 0.5%).^(R-117)

SULFAMETHOXAZOLE AND TRIMETHOPRIM TABLETS USP

Usual dose: See *Sulfamethoxazole and Trimethoprim Oral Suspension USP*.

Strength(s) usually available:

U.S.—^(R-119)

Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
400 mg of sulfamethoxazole and 80 mg of trimethoprim (Rx) [*Bactrim*; *Sepra*; GENERIC].
800 mg of sulfamethoxazole and 160 mg of trimethoprim (Rx) [*Bactrim DS*; *Sepra DS*; GENERIC].

Canada—

Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
100 mg of sulfamethoxazole and 20 mg of trimethoprim (Rx) [*Apo-Sulfatrim*].
400 mg of sulfamethoxazole and 80 mg of trimethoprim (Rx) [*Apo-Sulfatrim*; *Novo-Trimel*; GENERIC].
800 mg of sulfamethoxazole and 160 mg of trimethoprim (Rx) [*Apo-Sulfatrim DS*; *Novo-Trimel D.S.*; GENERIC].

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

USP requirements: Preserve in well-closed, light-resistant containers. Contain the labeled amounts, within ±7%. Meet the requirements for Identification, Dissolution (70% of each active ingredient in 60 minutes in 0.1 N hydrochloric acid in Apparatus 2 at 75 rpm), and Uniformity of dosage units.^(R-117)

Parenteral Dosage Forms

Note: The text between ^{EL,US} and ^{EL} describes uses not included in U.S. product labeling. Text between ^{EL,CAN} and ^{EL} describes uses that are not included in Canadian product labeling.

The ^{EL,US} or ^{EL,CAN} designation can signify a lack of product availability in the country indicated. See also the *Strength(s) usually available* section for each dosage form.

SULFAMETHOXAZOLE AND TRIMETHOPRIM INJECTION USP

Usual dose:

Note: ^{EL,US,CAN} Bacterial or protozoal infections—*Foals and horses*:

Although the efficacy and safety have not been established, a slow intravenous dose of 12.5 mg of sulfamethoxazole and 2.5 mg of trimethoprim per kg of body weight every twelve hours has been used in the treatment of susceptible bacterial and protozoal infections in foals and horses, based on pharmacokinetic data.^(R-31; 32) However, to reach effective concentrations in the cerebrospinal fluid (CSF) for bacterial and protozoal infections, higher doses are required; distribution studies show that an intravenous dose of 36 mg of sulfamethoxazole and 7.5 mg of trimethoprim per kg of body weight will produce CSF concentrations sufficient to treat susceptible bacterial and protozoal infections.^(R-31; 33) Intravenous doses should be administered slowly.^{EL}

Strength(s) usually available:

U.S.—^(R-2)

Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
80 mg of sulfamethoxazole and 16 mg of trimethoprim per mL (Rx) [GENERIC].

Canada—^(R-18)

Veterinary-labeled product(s):
Not commercially available.

Human-labeled product(s):
80 mg of sulfamethoxazole and 16 mg of trimethoprim per mL (Rx) [*Sepra*].

Packaging and storage: Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by the manufacturer. Store in a light-resistant container. Should not be refrigerated.

Preparation of dosage form: The contents of each vial (5 mL) must be diluted to 75 to 125 mL with 5% dextrose injection prior to administration by intravenous infusion.^(R-2) The resulting solution should be administered by intravenous infusion over a sixty- to ninety-minute period.

Stability: After initial dilution with 75 or 125 mL of 5% dextrose injection, infusion should be administered within two or six hours, respectively. The solution should not be used if it is cloudy or contains a precipitate. The solution should not be mixed with other medications or solutions.^(R-2)

USP requirements: Preserve in single-dose, light-resistant containers, preferably of Type I glass. May be packaged in 50-mL multiple-dose containers. A sterile solution of Sulfamethoxazole and Trimethoprim in Water for Injection which, when diluted with Dextrose Injection, is suitable for intravenous infusion. Label it to indicate that it is to be diluted with 5% Dextrose Injection prior to administration. Contains the labeled amounts, within ±10%. Meets the requirements for Identification, Pyrogen, pH (9.5–10.5), Particulate matter, and Related compounds, and for Injections.^(R-117)

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