PYRIMETHAMINE (Veterinary—Systemic)

A commonly used *brand name* for a human-labeled product is *Daraprim.*

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

Category:
Antiprotozoal (systemic).

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

General considerations
Pyrimethamine is a folic acid antagonist,{R-1} active against protozoal dihydrofolate reductase. It is considered most effective against pathogenic protozoa when administered in combination with a sulfonamide.{R-11; 16; 20}

The ready availability of combination products containing trimethoprim and sulfadiazine or trimethoprim and sulfamethoxazole may have contributed to the frequency of their concurrent administration with pyrimethamine. While trimethoprim does not increase the efficacy of therapy against protozoa,{R-30} it is suspected to increase the incidence of side effects due to folate reduction.{R-1; 21} Whenever possible, pyrimethamine should be administered in combination with a sulfonamide alone in the treatment of susceptible infections.

The development of resistant organisms has been stimulated in *in vitro* experiments, and cross-resistance by these cultures to other dihydrofolate inhibitors has been shown. However, when pyrimethamine was combined with a sulfonamide in the treatment of pyrimethamine-resistant *Neospora* cultures, the combination was completely effective.{R-11}

In the case of equine protozoal myeloencephalitis, resistance may occur within an individual horse if inadequate treatment is administered; however, transmission of resistance to the *Sarcocystis neurona* population outside the individual is not considered a problem because the horse is an aberrant host and does not shed infectious organisms.{R-21; 29}

Accepted
[EL]US,CAN Equine protozoal myeloencephalitis (treatment)[EL]—*Horses:* Pyrimethamine is used in combination with a sulfonamide, such as sulfadiazine or sulfamethoxazole,{R-9} in the treatment of protozoal myeloencephalitis.{R-7; 8; 21}

Potentially effective
[EL]US,CAN *Neospora caninum* infection (treatment)[EL]—*Dogs:* Although the efficacy and safety have not been established, pyrimethamine is used in combination with sulfonamides, most typically sulfadiazine, in the treatment of *Neospora caninum* infection. This use is based on evidence of *in vitro* pathogen susceptibility{R-11; 13} and case reports of successful treatment outcomes in some dogs, particularly in puppies in which clinical signs of the infection had not yet progressed to rigid hindlimb paralysis.{R-12; 14; 15}

[EL]US,CAN Toxoplasmosis (treatment)[EL]—*Cats:* Although the efficacy and safety have not been established, pyrimethamine is used in combination with sulfadiazine in the treatment of toxoplasmosis in cats.{R-18-20} Side effects associated with the administration of pyrimethamine and sulfadiazine have led clinicians to search for other treatments. However, this therapy may have some value in the treatment of infection with nonencysted organisms in cats that can tolerate the medications.

Regulatory Considerations
U.S. and Canada—Pyrimethamine is not labeled for use in animals, including food-producing animals; therefore, there are no established withdrawal times.

Chemistry
Chemical group: A diaminopyrimidine; structurally related to trimethoprim.{R-6}

Chemical name: 2,4-Pyrimidinediamine, 5-(4-chlorophenyl)-6-ethyl-.{R-2}

Molecular formula: $C_{12}H_{13}ClN_4$.{R-2}

Molecular weight: 248.71.{R-2}

Description: Pyrimethamine USP—White, odorless, crystalline powder.{R-3}

pka: 7.34.{R-5}

Solubility: Pyrimethamine USP—Practically insoluble in water; slightly soluble in acetone, in alcohol, and in chloroform.{R-3}

Pharmacology/Pharmacokinetics
Mechanism of action/Effect: Pyrimethamine reversibly binds to and inhibits the enzyme dihydrofolate reductase in protozoa. This inhibition prevents the production of tetrahydrofolic acid from dihydrofolate and thereby prevents the metabolism of folate.{R-6} Like protozoa, mammalian cells reduce folic acid to tetrahydrofolic acid; however, the therapeutic action of pyrimethamine relies on a greater selectivity for protozoal dihydrofolate reductase than for the mammalian enzyme.{R-1; 16} Pyrimethamine is generally administered in conjunction with a sulfonamide to take advantage of the sequential inhibition of enzymatic steps in folate synthesis provided by the combination.{R-1}

Absorption: Oral—*Human beings:* Pyrimethamine is well absorbed orally.{R-1}

Bioavailability: Oral—*Horses:* Average, 56% (range, 39 to 78%).{R-5}

Distribution: Rapidly and extensively distributed after intravenous administration.{R-5}

Horses—Cerebrospinal fluid (CSF) concentrations reached 25 to 50% of the serum concentrations but did not appear to accumulate in horses administered daily oral doses of 1 mg per kg of body weight (mg/kg) for 10 days.{R-6}

Pigs—Distribution occurs in two phases after a 10 mg/kg intravenous dose; the fast phase has a half-life of 0.11 hour, and the slow phase has a half-life of 1.6 hours.{R-10}

Rats—Mean CSF concentration was 27% of the plasma concentration during the first 48 hours after a single oral dose of 2.9 mg/kg (1 mg per rat).{R-24}

Volume of distribution—Intravenous administration:

Horses—Steady-state: 1.52 liters per kg (L/kg).{R-5}

Pigs—Area: 12.1 ± 2 L/kg.{R-10}

Protein binding:

Dogs—85%.{R-24}

Human beings—87%.{R-24}

Mice—78%.{R-24}

Pigs—85%, independent of serum concentration.{R-10}

Rats—78%.{R-6}

Biotransformation: Less than 5% of administered doses are excreted as unchanged drug in the urine in pigs{R-10} and rats;{R-24} five hours after administration of radiolabeled pyrimethamine to a

rat, less than 50% of radioactivity in the blood was intact parent drug.[R-24] Therefore, it is believed that pyrimethamine is extensively metabolized, although metabolites have not been identified in animals. In human beings, pyrimethamine is believed to be hepatically metabolized.[R-24; 28]

Half-life: Elimination—Intravenous administration:
Horses—12 ± 3.7 hours.[R-5]
Pigs—13.3 ± 4.9 hours.[R-10]

Concentrations:
Peak serum concentration—Oral administration: *Horses*—
Single dose: 0.18 ± 0.03 mcg per mL of serum (mcg/mL) with administration of 1 mg/kg[R-5]
Multiple doses: 0.32 ± 0.11 mcg/mL after the 5th dose and 0.26 ± 0.07 mcg/mL after the 10th dose of 10 daily doses of 1 mg/kg.[R-6]
Time to peak concentration—Oral administration: *Horses*—
Single dose: 2.9 ± 2.1 hours after administration of 1 mg/kg.[R-5]
Multiple doses: 2.2 hours after the 5th dose and 2.7 hours after the 10th dose of 10 daily doses of 1 mg/kg.[R-6]
Serum concentrations, other—Oral administration: *Horses*—
Single dose: 0.09 mcg/mL 24 hours after administration of 1 mg/kg.[R-5]
Multiple doses: Plasma steady state was reached at the 5th day of 10 daily doses of 1 mg/kg; at that time the serum concentrations fluctuated approximately 65% over each 24-hour period, with the peak at approximately 0.32 mcg/mL.[R-6]

Elimination: *Pigs*—Only about 3% of an intravenous dose of pyrimethamine is excreted in the urine as unchanged drug, although up to 90% of the dose is eliminated in that time.[R-10]
Total clearance—
Horses: 1.6 ± 0.32 mL per minute per kg (mL/min/kg).[R-5]
Pigs: 0.68 ± 0.16 mL/min/kg.[R-10]

Precautions to Consider

Carcinogenicity
Mice: A significant increase in the number of lung tumors per mouse has been reported with doses of 25 mg per kg of body weight (mg/kg), administered intraperitoneally.[R-1]

Pregnancy/Reproduction
Reproduction: *Rats*—The fertility index of rats treated with pyrimethamine is lowered only by the highest doses administered. This suggests a toxic effect on the whole animal or the conceptus.[R-1]
Pregnancy:
Hamsters—Single doses of 20 mg per pregnant hamster caused malformation or death in less than 10% of fetuses.[R-1]
Horses—In a group of horses treated with oral pyrimethamine at 1 mg per kg of body weight (mg/kg) a day, sulfadiazine at 16.7 mg/kg every twelve hours, and trimethoprim at 3.3 mg/kg every twelve hours, the three horses that were pregnant during therapy aborted during the second or third month of treatment.[R-21] Each of the aborted fetuses was in the fifth month of gestation.[R-21] It is not certain which of the medications might have caused the abortions. The horses' diets had not been supplemented with folate at the time of the abortions.[R-21]
The administration of oral folic acid to pregnant mares being treated for equine protozoal myeloencephalitis may not protect the fetus from the effects of folate deficiency. Reports have been made of mares delivering foals with congenital defects after oral administration during pregnancy of pyrimethamine, 0.5 to 1 mg/kg a day, with sulfadiazine, 25 mg/kg a day; or sulfamethoxazole, 12.5 mg/ kg day, and trimethoprim, 2.5 mg/kg.[R-35] Two of the three reported mares had been treated in the last 3 months of gestation and one for 2 years before foaling. These mares had also been supplemented with oral folic acid, 40 mg as a total daily dose, and vitamin E, 8000 Units as a total daily dose, during the period of antibiotic treatment. Each of three mares on this dosage regimen produced a foal with renal hypoplasia or nephrosis and bone marrow aplasia or hypoplasia.[R-35] In both mares and foals, serum folate concentrations were below the laboratory reference range and in two foals, folate was less than 30% of the minimum reference range.[R-35] The risk of congenital defects should be considered when treating pregnant mares with pyrimethamine and sulfonamide.
Miniature pigs—A high incidence of malformations (70%), such as cleft palate, club foot, and micrognathia, was seen in offspring when pregnant sows were administered pyrimethamine, 3.6 mg/kg a day, from days 11 to 35 of gestation; however, no abnormalities were noted in the offspring of sows administered 0.9 to 1.8 mg/kg a day during the same period of gestation.[R-1; 4]
Rats—Fetal resorption and stunted growth in fetuses have been seen in pregnant rats given pyrimethamine.[R-1] Rats administered 12.5 mg/kg from days 7 to 9 of gestation had 66% of fetuses resorbed and 33% stunted, while a dose of 0.5 to 1 mg/kg from days 4 to 13 of gestation caused resorption of 8 to 15% of fetuses and stunted growth in 7 to 17% of fetuses.[R-1]

Lactation
Pyrimethamine is distributed into human milk.[R-1] Distribution into milk in lactating animals has not been determined.

Pediatrics
Dogs: Pyrimethamine has been administered at a dose of 1 mg per kg of body weight a day for 4 weeks in 8- to 17-week-old puppies, without any apparent harmful effects.[R-14]

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: Drug interactions relating specifically to the use of pyrimethamine in animals are rarely reported in veterinary literature. Human drug interactions have been reported and are included in the following section.

Human drug interactions and/or related problems[R-37]
The following drug interactions have been reported in humans, and are included in the human monograph *Pyrimethamine (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 pyrimethamine in the treatment of animals:
Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
Bone marrow depressants
(concurrent use with pyrimethamine may increase the risk of bone marrow suppression)
Folate antagonists, other
(concurrent use of other folate antagonists with pyrimethamine or use of pyrimethamine between courses of other folate antagonists is not recommended because of the possible development of megaloblastic anemia)

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:

» Anemia or
Bone marrow suppression
(pyrimethamine may cause folate deficiency, resulting in megaloblastic anemia and blood dyscrasias, including agranulocytosis and thrombocytopenia)[R-19; 21; 26]

» Hepatic function impairment, severe
(in human beings, pyrimethamine is metabolized in the liver)

Risk-benefit should be considered when the following medical problem exists:
Pregnancy
(the risk of teratogenesis should be considered in planning treatment with pyrimethamine)[R-35]

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 counts (CBCs)[R-19; 21; 23] and
Platelet counts
(should be performed on a regular basis, particularly with long-term or high-dose therapy; periodic packed cell volume evaluation is recommended in horses being treated for equine protozoal myeloencephalitis to monitor for anemia[R-29])

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:

Note: It is assumed that animals have the same tendency as people to develop signs of *folate deficiency* with long-term use or high doses of folic acid antagonists such as pyrimethamine. Signs of folate deficiency have been reported frequently in the human literature and include agranulocytosis, megaloblastic anemia, and thrombocytopenia.[R-16] Similar signs have been noted in cats, dogs, and horses.[R-19; 21; 26] It should be considered that signs of folate deficiency may occur in any species administered pyrimethamine. When administering pyrimethamine with a sulfonamide, the risk of sulfonamide-related side effects should be considered. See the *Sulfonamides (Veterinary—Systemic)* monograph for further information.

Those indicating need for medical attention

Incidence unknown

Cats

Leukopenia—seen with a dose of 1 mg per kg of body weight (mg/ kg) a day for 6 days[R-19]

Horses

Anemia;[R-21] ***congenital defects in offspring*** (bone marrow aplasia or hypoplasia; renal nephrosis or hypoplasia; skin lesions);[R-35] ***diarrhea;***[R-21] ***leukopenia***[R-21]

Human side/adverse effects[R-37]

In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans, and are included in the human monograph *Pyrimethamine (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 pyrimethamine in the treatment of animals:

Incidence less frequent

Agranulocytosis, leukopenia, or thrombocytopenia; atrophic glossitis; gastrointestinal disturbances (anorexia, diarrhea, nausea, and vomiting)

Incidence rare

Erythema multiforme and/or Stevens-Johnson syndrome; hypersensitivity

Incidence unknown

Anaphylaxis; cardiac arrythmia; hematuria; megaloblastic anemia; pancytopenia; pulmonary eosinophilia; toxic epidermal necrolysis

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.**

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:

Dogs—with a dose of 5 to 10 mg per kg of body weight (mg/kg) a day for 10 to 21 days[R-26]

Chronic effects

Anorexia and/or decreased appetite; ataxia; bone marrow suppression, including leukopenia and reticulocytopenia; dehydration; gastrointestinal toxicity (diarrhea, occasionally bloody; vomiting); ***weakness; weight loss***

Note: Respiratory depression and circulatory collapse, as well as neurotoxicity leading to seizures, have been reported in people receiving total doses of 250 to 300 mg of pyrimethamine.[R-1] These specific signs have not been reported in animals; however, one of four dogs administered 5 mg/kg a day died on the 17th day of therapy; the specific cause of death was not reported.[R-26]

Bone marrow suppression has been demonstrated by biopsy in a few dogs receiving extremely high doses of pyrimethamine (6 mg/kg a day for 10 to 15 days).[R-26] Three of eight dogs treated had bone marrow suppression, particularly of the erythroid elements.[R-26]

In dogs, *vomiting* was reported to be common within 2 to 5 hours of administration of 7.5 to 10 mg/kg, but vomiting was seen only occasionally in dogs receiving 5 mg/kg a day for 10 to 21 days.[R-26] Intestinal lesions, including inflammation, mucoid degeneration, shortened villi and mucosal atrophy, are visible on histopathologic examination after administration of 6.2 mg/kg a day for 10 days to dogs.[R-26]

Treatment of overdose[R-1]

- Gastric lavage.
- Control of central nervous system stimulation by administration of benzodiazepines or short-acting barbiturates, if necessary.
- Respiratory assistance, if necessary.
- Administration of folate to mitigate hematopoietic changes (see *Veterinary Dosing Information*).

Client Consultation

Clients should be advised to watch for signs such as loss of appetite, weakness, pale mucous membranes or pinpoint blood spots in membranes, or noticeable bruising.

General Dosing Information

The administration of sulfadiazine and trimethoprim products labeled for use in animals in combination with human-labeled pyrimethamine tablets has been commonly discussed in veterinary literature. However, the low affinity of protozoal dihydrofolate for trimethoprim suggests poor efficacy of trimethoprim in the treatment of protozoal infections.[R-30] The concurrent administration of trimethoprim with pyrimethamine offers no known benefit and may increase the risk of adverse effects associated with these dihydrofolate reductase inhibitors.[R-1; 9; 21] Whenever possible, pyrimethamine should be administered in combination with a sulfonamide alone in the treatment of susceptible infections.

The administration of folic acid or folinic acid supplements during treatment with pyrimethamine may help to prevent adverse effects associated with folate deficiency, which occur as an extension of the mechanism of action of the drug;[R-9; 21] however, neither oral supplement has been clearly proven to be effective. Only limited information on the effectiveness of folic acid or folinic acid in the prevention of folate deficiency caused by pyrimethamine is available.

Cats and *dogs:* No definitive studies are available to confirm that folic acid or folinic acid supplementation should be used to prevent signs of folate deficiency that may occur during treatment with pyrimethamine.[R-36] Monitoring animals for signs of folate deficiency is recommended during treatment with pyrimethamine (see the *Patient monitoring* and *Side/Adverse Effects* sections).[R-36]

Horses: An oral folic acid dose of 0.09 to 0.18 mg/kg (40 to 80 mg per horse) every twenty-four hours has been used;[R-29; 31] however, case reports have shown that a total dose of 40 mg of folic acid a day given to pregnant mares being treated with pyrimethamine and sulfonamide is sometimes not effective in preventing congenital defects in foals caused by folate deficiency.[R-35] Fresh grass has more than twice the total folacin concentration of hay,[R-32] and serum folate concentrations tend to be much higher in pastured horses than in permanently stabled horses or horses in training.[R-33; 34] It has been recommended that horses be maintained on feeds containing high folacin concentrations during pyrimethamine therapy.[R-29] Rather than supplementing horses with folic acid, some clinicians recommend monitoring the packed-cell volume to detect developing anemias.

Some clinicians have used the *in vitro* minimum inhibitory concentration (MIC) of pyrimethamine necessary to inhibit *Toxoplasma gondii*[R-5; 21] or the MIC of pyrimethamine necessary to inhibit *Neospora caninum*[R-11] as guidelines for target cerebrospinal fluid concentrations for control of the *Sarcocystis* species responsible for equine protozoal myeloencephalitis.[R-5]

Diet/Nutrition

Horses: Pyrimethamine should be administered 1 hour prior to feeding hay.[R-9]

Human beings: Information from human product labeling includes the statement that anorexia and vomiting induced by pyrimethamine may be minimized by administering it with food.[R-1]

Oral Dosage Forms

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

PYRIMETHAMINE TABLETS USP

Usual dose:

EL[US,CAN] Equine protozoal myeloencephalitis—*Horses:* Oral, 1 mg per kg of body weight every twenty-four hours,[R-5] in combination with 16.7 mg of sulfadiazine or sulfamethoxazole per kg of body weight every twelve hours, has been used.[R-5; 8; 9; 21] The average duration of treatment necessary to clear the organism may be as long as 130 days or more.[R-21] Testing cerebrospinal fluid for *Sarcocystis neurona* antibodies may help determine when to discontinue treatment.EL[R-21]

Withdrawal times—U.S. and Canada: Pyrimethamine is not labeled for use in animals, including food-producing animals; therefore, there are no established withdrawal times.

EL[US,CAN] *Neospora caninum* infection—*Dogs:* Although the efficacy and safety have not been established, an oral dose of 1 mg of pyrimethamine per kg of body weight every twenty-four hours, in combination with 12.5 mg of sulfadiazine per kg of body weight every twelve hours, for four weeks has been used.EL[R-14]

Note: The above dosages for dogs and horses are based on clinical case reports with successful outcomes that also included the concurrent administration of trimethoprim, a practice that is generally not recommended. To decrease the risk of toxicity, the administration of pyrimethamine with sulfadiazine alone is preferred, but there are no reports of the efficacy of this combination.

EL[US,CAN] Toxoplasmosis—*Cats:* Although the efficacy and safety have not been established, an oral dose of 1 mg of pyrimethamine per kg of body weight every twenty-four hours, in combination with 25 mg of sulfadiazine per kg of body weight every twelve hours, for fourteen to twenty-eight days has been used.EL[R-18]

Note: The above dose was extrapolated from studies evaluating the efficacy of pyrimethamine and sulfadiazine in ending or reducing shedding of oocysts as well as preventing tissue infection.[R-18; 19]

Because pyrimethamine is only available in 25-mg tablets, some clinicians arrange for capsules to be formulated in smaller strengths for easier administration of the unpalatable medication to cats. Consultation with an experienced pharmacist is recommended.

Strength(s) usually available:

U.S.—

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

Human-labeled product(s):[R-1]
25 mg (Rx) [*Daraprim* (scored)].

Canada—

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

Human-labeled product(s):
25 mg (Rx) [*Daraprim* (scored)].

Packaging and storage: Store below 40 ºC (104 ºF), preferably between 15 and 30 ºC (59 and 86 ºF), unless otherwise specified by manufacturer. Store in a tight, light-resistant container.

Auxiliary labeling: • Keep out of the reach of children.[R-1]

Caution: Potential danger of accidental overdose.[R-1]

USP requirements: Preserve in tight, light-resistant containers. Contain the labeled amount, within ± 7%. Meet the requirements for Identification, Dissolution (75% in 45 minutes in 0.01 *N* hydrochloric acid in Apparatus 2 at 50 rpm), and Uniformity of dosage units.[R-3]

Developed: 07/01/98
Interim revision: 10/14/99; 9/30/02; 03/28/03; 06/30/07

References

1. Pyrimethamine package insert (Daraprim, Burroughs Wellcome—US), Rev 4/94, Rec 10/13/94.
2. USP dictionary of USAN and international drug names, 2006 ed. Rockville, MD: The United States Pharmacopeial Convention, Inc., 2006.
3. The United States pharmacopeia. The national formulary. USP 30th revision (May 1, 2007). NF 25th ed (May 1, 2007). Rockville, MD: The United States Pharmacopeial Convention, Inc., 2006.
4. Misawa J, Kanda S, Kokue E, et al. Teratogenic activity of pyrimethamine in Gottingen minipig. Toxicol Lett 1982; 10(1): 51-4.
5. Clarke CR, Burrows GE, MacAllister CG, et al. Pharmacokinetics of intravenously and orally administered pyrimethamine in horses. Am J Vet Res 1992 Dec; 53(12): 2292-5.
6. Clarke CR, Burrows GE, MacAllister CG, et al. Pharmacokinetics, penetration into cerebrospinal fluid, and hematologic effects after multiple oral administrations of pyrimethamine to horses. Am J

Vet Res 1992 Dec; 53(12): 2296-9.
7. Boy MG, Galligan DT, Divers TJ. Protozoal encephalomyelitis in horses: 82 cases (1972-1986). J Am Vet Med Assoc 1990 Feb; 196(4): 632-4.
8. Brewer B, Mayhew IG. Multifocal neurologic disease in a horse. J Equine Vet Sci 1988 Jul/Aug; 8(4): 302-4.
9. Bertone JJ. Update on equine protozoal myeloencephalitis. FDA Vet 1996 May/Jun; XI(III): 7-9.
10. Shimoda M, Kokue E, Kurebayashi Y, et al. Three-compartment model for pyrimethamine disposition in the pig. J Vet Pharmacol Ther 1981 Jun; 4(2): 165-70.
11. Lindsay DS, Butler JM, Rippey NS, et al. Demonstration of synergistic effects of sulfonamides and dihydrofolate reductase/thymidylate synthase inhibitors against Neospora caninum tachyzoites in cultured cells, and characterization of mutants resistant to pyrimethamine. Am J Vet Res 1996 Jan; 57(1): 68-72.
12. Knowler C, Wheeler SJ. Neospora caninum infection in three dogs. J Small Anim Pract 1995; 36: 172-7.
13. Lindsay DS, Rippey NS, Cole RA, et al. Examination of the activities of 43 chemotherapeutic agents against Neospora caninum tachyzoites in cultured cells. Am J Vet Res 1994 Jul; 55(7): 976-81.
14. Mayhew IG, Smith KC, Dubey JP, et al. Treatment of encephalomyelitis due to Neospora caninum in a litter of puppies. J Small Anim Pract 1991; 32: 609-12.
15. Hay WH, Shell LG, Lindsay DS, et al. Diagnosis and treatment of Neospora caninum infection in a dog. J Am Vet Med Assoc 1990 Jul 1; 197(1): 87-8.
16. St. Georgiev V. Opportunistic/nosocomial infections. Treatment and developmental therapeutics. Toxoplasmosis. Med Res Rev 1993 Sep; 13(5): 529-68.
17. Davidson MG, Lappin MR, Rottman JR, et al. Paradoxical effect of clindamycin in experimental, acute toxoplasmosis in cats. Antimicrob Agents Chemother 1996 Jun; 40(6): 1352-9.
18. Sheffield HG, Melton ML. Effects of pyrimethamine and sulfadiazine on the intestinal development of Toxoplasma gondii in cats. Am J Trop Med Hyg 1976 May; 25(3): 379-83.
19. Dubey JP, Yeary RA. Anticoccidial activity of 2-sulfa-moyl-4,4-diaminodiphenylsulfone, sulfadiazine, pyrimethamine and clindamycin in cats infected with Toxoplasma gondii. Can Vet J 1977 Mar; 18(3): 51-7.
20. Mack DG, McLeod R. New micromethod to study the effect of antimicrobial agents on Toxoplasma gondii: comparison of sulfadoxine and sulfadiazine individually and in combination with pyrimethamine and study of clindamycin, metronidazole, and cyclosporin A. Antimicrob Agents Chemother 1984 Jul; 26(1): 26-30.
21. Fenger CK, Granstom DE, Langemeier JL, et al. An epizootic of equine protozoal myeloencephalitis on a farm. J Am Vet Med Assoc 1997 Apr 1; 210(7): 923-7.
22. McCabe RE, Oster S. Current recommendations and future prospects in the treatment of toxoplasmosis. Drugs 1989 Dec; 38(6): 973-87.
23. Peterson JL, Willard MD, Lees GE, et al. Toxoplasmosis in two cats with inflammatory intestinal disease. J Am Vet Med Assoc 1991 Aug; 199(4): 473-6.
24. Cavallito JC, Nichol CA, Brenckman WD, et al. Lipid-soluble inhibitors of dihydrofolate reductase. I. Kinetics, tissue distribution, and extent of metabolism of pyrimethamine, metoprine, and etoprine in the rat, dog, and man. Drug Metab Dispos 1978; 6: 329-37.
25. Bygbjerg IC, Lund JT, Hording M. Effect of folic and folinic acid on cytopenia occurring during cotrimoxazole treatment of pneumocystis carinii pneumonia. Scand J Infect Dis 1988; 20: 685-6.
26. Castles TR, Kintner LD, Lee C. The effects of folic or folinic acid on the toxicity of pyrmethamine in dogs. Toxicol Appl Pharmacol 1971; 20: 447-59.
27. Plumb DC. Veterinary drug handbook, 2nd ed. Ames, IA: Iowa University Press, 1995. p. 541-3.
28. Weiss LM, Harris C, Berger M, et al. Pyrimethamine concentrations in serum and cerebrospinal fluid during treatment of acute toxoplasma encephalitis in patients with AIDS. J Infect Dis 1988 Mar; 157(3): 580-3.
29. Reviewer comment, Rec 7/11/97.
30. Panel comment, Rec 6/22/97.
31. Reviewer comment, Rec 6/18/97.
32. National Research Council. Nutrient requirements of horses. Washington, D.C.: National Academy Press, 1989. p. 29-30.
33. Roberts MC. Serum and red cell folate and serum levels in horses. Aust Vet J 1983 Apr; 60(4): 106-11.
34. Allen BV. Serum folate levels in horses, with particular reference to the English thoroughbred. Vet Rec 1978; 103: 257-9.
35. Toribio RE, Bain FT, Mrad OR, et. al. Congenital defects in newborn foals of mares treated for equine protozoal myeloencephalitis during pregnancy. J Am Vet Med Assoc 1998 Mar 1; 212(5): 697-701.
36. Panel consensus, 5/5/98.
37. Klasco RK, editor. USP DI Drug information for the healthcare professional. Volume I. Greenwood Village, CO: MICROMEDEX, Inc.; 2006. Available at www.thomsonhc.com. Accessed on December 4, 2006.

