■ **HORSES:**

See also the next monograph (Pyrimethamine + Sulfadiazine)
For equine protozoal myeloencephalitis:

a) Pyrimethamine 1 mg/kg PO once a day for 90–120 days (or longer). Given with a sulfa or potentiated sulfa (sulfadiazine 20 mg/kg PO once or twice a day). Monitor: CBC's (Moore 1999); (MacKay, Granstrom et al. 2000)

■ **BIRDS:**

For Coccidian organisms in raptors:

a) 0.5 mg/kg PO twice daily for 14–28 days (especially effective against Toxoplasmosis, Atoxoplasmosis and Sarcocystis). (Jones 2007b)

Monitoring

- See adverse effects; CBC with platelet count
- Clinical efficacy

Client Information

- Clients should he instructed to monitor for clinical signs of abnormal bleeding, lassitude, etc. that may signal development of hematologic disorders.
- Accurate dosing of the tablets in cats may be very difficult as only 25 mg tablets are commercially available. Preferably, custom prepared capsules containing the accurate dosage should be prepared.

Chemistry/Synonyms

An aminopyrimidine agent structurally related to trimethoprim, pyrimethamine occurs as an odorless, white, or almost white, crystalline powder or crystals. It is practically insoluble in water and slightly soluble in alcohol.

Pyrimethamine may also be known as: BW-50-63, pirimetamina, pyrimethaminum, RP-4753, *Daraprim*®, *Malocide*®, or *Pirimecidan*®.

Storage/Stability/Compatibility

Pyrimethamine tablets should be stored in tight, light-resistant containers.

Pyrimethamine tablets may be crushed to make oral suspensions of the drug. Although stable in an aqueous solution, sugars tend to adversely affect the stability of pyrimethamine. If cherry syrup, corn syrup, or sucrose-containing liquids are used in the preparation of the suspension, it is recommended to store the suspension at room temperature and discard after 7 days.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Pyrimethamine Tablets: 25 mg; *Daraprim*® (GlaxoSmithKline); (Rx)

PYRIMETHAMINE + SULFADIAZINE

(pye-ri-***meth***-a-meen + sul-fa-***dye***-a-zeen) ReBalance®

ANTIPROTOZOAL

Note: Also see the Pyrimethamine, and Sulfadiazine/Trimethoprim monographs

Prescriber Highlights

- Tetrahydrofolic acid inhibitor suspension labeled for the treatment of horses with equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona*
- May cause bone marrow suppression, GI effects, & "treatment crisis" (patient's signs worsen after beginning therapy)
- Daily treatment may be required for 3–9 months

Uses/Indications

ReBalance® (pyrimethamine/sulfadiazine suspension in a 1:20 concentration) is labeled for the treatment of horses with equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona*. Although not labeled for use in small animals it potentially could be useful for treating protozoal infections such as Toxoplasmosis in cats or Neosporosis in dogs.

Pharmacology/Actions

Sulfonamides inhibit the conversion of para-aminobenzoic acid (PABA) to dihydrofolic acid (DFA) by competing with PABA for dihydropteroate synthase. Pyrimethamine blocks the conversion of DFA to tetrahydrofolic acid by inhibiting dihydrofolate reductase. When sulfas and dihydrofolate reductase inhibitors (*e.g.*, trimethoprim, pyrimethamine) are used together, synergistic effects can occur. When comparing pyrimethamine and trimethoprim, pyrimethamine is more active against protozoal dihydrofolate reductase and trimethoprim is more active against bacterial dihydrofolate reductase.

Pharmacokinetics

No specific information was located for the pharmacokinetics of this drug combination and dosage form (oral suspension) in horses. Previous reports in horses using other dosage forms reported pyrimethamine oral bioavailability of approximately 56% and elimination half-life of about 12 hours. CNS levels are approximately 25–50% of those found in plasma. Sulfadiazine is apparently well absorbed after oral administration to horses and enters the CSF. Volume of distribution is approximately 0.58 L/kg; elimination half-life is about 3–4 hours.

Contraindications/Precautions/Warnings

This drug combination is contraindicated in horses hypersensitive to either pyrimethamine or sulfadiazine. It should not be used in horses intended for human consumption. Because it may cause bone marrow suppression, use with caution in horses with preexisting hematologic abnormalities or those receiving other drugs that may cause bone marrow suppression.

Adverse Effects

Adverse effects in horses reported during field trials for pyrimethamine/sulfadiazine suspension include bone marrow suppression (anemia, leukopenia, neutropenia, thrombocytopenia),

reduced appetite/anorexia, loose stools/diarrhea, and urticaria. CNS effects may be noted (seizures, depression), but are probably a result of the disease (EPM).

Baker's yeast or folinic acid have been suggested to antagonize the drug combination's bone marrow depressive effects, but efficacy has not been proven.

During the initial period (first few days) of treatment, neurologic signs may worsen—so-called treatment crisis—and may persist up to 5 weeks. It is thought this may be the result of an inflammatory reaction secondary to dying parasites in the central nervous system.

Reproductive/Nursing Safety

The label for *ReBalance*® (pyrimethamine/sulfadiazine suspension) states that the safe use of this product in horses for breeding purposes, during pregnancy, or in lactating mares has not been evaluated. Pyrimethamine has been demonstrated to be teratogenic in rats. Fetal abnormalities have been seen in foals after mares have been treated; however, it has been used in treating women with toxoplasmosis during pregnancy. Risks associated with therapy must be weighed against the potential for toxicity, the severity of the disease, and any alternative therapies available. Some have recommended concomitant administration of folinic acid if the drug is to be used during pregnancy, but others state that pregnant mares should not receive folic acid during therapy as it may exacerbate fetal abnormalities or mortality. In humans, the FDA categorizes pyrimethamine as category ***C*** for use during pregnancy (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.*)

Sulfas cross the placenta and fetal serum levels may be up to 50% of that found in maternal serum. Teratogenicity has been reported in some laboratory animals when given at very high doses. Sulfas should be used in pregnant animals only when the benefits clearly outweigh the risks of therapy.

Sulfonamides are distributed into milk. Pyrimethamine is excreted in maternal milk and safety for nursing offspring has not been established; consider using milk replacer.

Overdosage/Acute Toxicity

Acute overdosage information for pyrimethamine/sulfadiazine in horses (greater than 2X) was not located. *ReBalance*® (pyrimethamine/sulfadiazine suspension) was administered at 2X the labeled dose for 92 days to 49 horses. Signs noted included loose stools, slight increases in ALP in some horses, declines in RBC, HCT, Hgb, and PCV, and depressed appetite.

Drug Interactions

The label for *ReBalance*® (pyrimethamine/sulfadiazine suspension) states that the safety of this product with concomitant therapies in horses has not been evaluated.

In humans, the following drug interactions with sulfas and/or pyrimethamine have been reported or are theoretical and may be of significance in veterinary patients:

- **ANTACIDS**: May decrease the bioavailability of sulfonamides if administered concurrently
- **HIGHLY PROTEIN-BOUND DRUGS** (*e.g.,* **methotrexate, phenylbutazone, thiazide diuretics, salicylates, probenecid, phenytoin, warfarin**): Sulfonamides may displace other highly bound drugs
- **p-AMINOBENZOIC ACID** (**PABA**): PABA is reportedly antagonistic towards the activity of pyrimethamine; clinical significance is unclear
- **TRIMETHOPRIM**: Use with pyrimethamine/sulfa is not recommended in humans as adverse effects may be additive, however, this combination has been used clinically in horses

Laboratory Considerations

The following laboratory alterations have been reported in humans taking sulfonamides and may be of significance in veterinary patients:

- **Urine glucose**: Sulfonamides may give false-positive results when using the Benedict's method

Doses

- **HORSES:**

For treatment of EPM:

a) 20 mg/kg sulfadiazine with 1 mg/kg pyrimethamine; equivalent to 4 mL of *ReBalance*® suspension per 50 kg (110 lb) body weight PO once daily at least 1 hour before feeding with hay or grain. Administer using a suitable oral dosing syringe; insert nozzle through the interdental space and deposit the dose on the back of the tongue by depressing the plunger. Treatment duration is based upon clinical response, but usually ranges from 90–270 days. (Label information; *ReBalance*®—Phoenix)

Monitoring

- CBC (including platelets): baseline and at least monthly during therapy
- GI adverse effects
- Clinical Efficacy: Improvement in neuro signs, CSF Western Blot test negative

Client Information

- Shake well before using and store at room temperature; see dosage information for instructions on proper administration
- Horse may develop worsening signs after beginning treatment, probably due to local inflammation from dying parasites
- Watch for signs that may indicate toxicity including depression, bleeding, bruising, bloody diarrhea, etc.; contact veterinarian if these occur

Chemistry/Synonyms

Pyrimethamine is an aminopyrimidine agent structurally related to trimethoprim. It occurs as an odorless, white, or almost white, crystalline powder or crystals. It is practically insoluble in water and slightly soluble in alcohol.

Sulfadiazine occurs as an odorless or nearly odorless, white to slightly yellow powder. It is practically insoluble in water and sparingly soluble in alcohol.

Sulfadoxine and Pyrimethamine may also be known as *Fansidar*® and *ReBalance*®.

Storage/Stability

ReBalance® suspension should be stored at controlled room temperature (15–30°C) and protected from freezing.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Sulfadiazine (as the sodium salt) 250 mg/mL and Pyrimethamine 12.5 mg/mL Oral Suspension in quart (946.4 mL) bottles; *ReBalance*® *Antiprotozoal Oral Suspension* (Phoenix); (Rx) Approved for use in horses; not for use in horses intended for human consumption.

HUMAN-LABELED PRODUCTS:

A related compound for humans is: Sulfadoxine & Pyrimethamine Tablets: 500 mg sulfadoxine & 25 mg pyrimethamine; *Fansidar®* (Roche); (Rx)

QUINACRINE HCL

(***qwin***-a-krin)

ANTIPROTOZOAL

Prescriber Highlights

- Antiprotozoal that may be useful for treatment of Giardia, Leishmania, & coccidia. May improve clinical signs associated with giardial infection, but not eliminate infection
- Contraindications: Potentially, if hepatic dysfunction or pregnancy
- Adverse Effects: Yellowing of skin & urine color, (not of clinical importance); GI (anorexia, nausea, vomiting, diarrhea), abnormal behaviors ("fly biting", agitation), pruritus, & fever. Potentially: Hypersensitivity, hepatopathy, aplastic anemia, corneal edema, & retinopathy.
- Availability an issue
- Potential teratogen
- Give with meals; have liquid available

Uses/Indications

While quinacrine has activity against a variety of protozoans and helminths, its use against all but Giardia and Trichomonas has been superseded by safer or more effective agents. In humans, quinacrine may be used for treatment of mild to moderate discoid lupus erythromatosis, transcervically as a sterilizing agent, or in powder form as an intrapleural sclerosing agent.

Pharmacology/Actions

Quinacrine's mechanism of action for its antiprotozoal activity against Giardia is not understood, however, it does bind to DNA by intercalation to adjacent base pairs thereby inhibiting RNA transcription and translocation. Additionally, quinacrine interferes with electron transport and inhibits succinate oxidation and cholinesterase. Quinacrine binds to nucleoproteins that (in humans at least) can suppress lupus erythromatosis (LE) cell factor.

Pharmacokinetics

Quinacrine is absorbed well from the GI tract or after intrapleural administration. It is distributed throughout the body, but CSF levels are only 1–5% of those found in plasma. Drug is concentrated in the liver, spleen, lungs, and adrenals. It is relatively highly bound to plasma proteins in humans (80–90%). Quinacrine crosses the placenta, but only small amounts enter maternal milk.

Quinacrine is eliminated very slowly (half life in humans: 5–14 days). Quinacrine is slowly metabolized, but primarily eliminated by the kidneys; acidifying the urine will increase renal excretion somewhat. Significant amounts may be detected in urine up to 2 months after drug discontinuation.

Contraindications/Precautions/Warnings

In humans, quinacrine is relatively contraindicated in patients with psychotic disorders, psoriasis, or porphyria as it may exacerbate these conditions. Veterinary relevance is unknown. The drug should be used with extreme caution in patients with hepatic dysfunction.

Adverse Effects

In small animals, a yellowing of skin and urine color can occur, but is not of clinical importance (does not indicate jaundice). Additionally, gastrointestinal disturbances (anorexia, nausea, vomiting, diarrhea), abnormal behaviors ("fly biting", agitation), pruritus, and fever have been noted.

Potentially hypersensitivity reactions, hepatopathy, aplastic anemia, corneal edema, and retinopathy could occur (all reported rarely in humans, primarily with high dose long-term use).

Reproductive/Nursing Safety

Quinacrine crosses the placenta and has been implicated in causing a case of renal agenesis and hydrocephalus in a human infant. In high doses, it has caused increased fetal death rates in rats. Weigh the potential benefits with the risks when considering use in pregnant animals.

In humans, the FDA categorizes this drug as category ***C*** for use during pregnancy (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.*)

Overdosage/Acute Toxicity

Overdosage may be serious depending on the dose. In humans, a dose as low as 6.8 grams (administered intraduodenally) caused death. Clinical signs associated with acute toxicity include CNS excitation (including seizures), GI disturbances, vascular collapse, and cardiac arrhythmias. Treatment consists of gut emptying protocols, and supportive and symptomatic therapies. Urinary acidification with ammonium chloride and forced diuresis (with adequate fluid therapy) may be beneficial in enhancing urinary excretion of the drug.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving quinacrine HCl and may be of significance in veterinary patients:

- **ALCOHOL**: Quinacrine may cause a "disulfiram-reaction" if used with alcohol.
- **HEPATOTOXIC DRUGS**: Quinacrine concentrates in the liver and should be used with caution with hepatotoxic drugs (clinical significance unknown).
- **PRIMAQUINE**: Quinacrine increases the toxicity of primaquine (generally not used in veterinary medicine), and the two should not be used simultaneously.

Laboratory Considerations

- When urine is acidic, quinacrine can cause it to turn a deep yellow color. By causing an interfering fluorescence, quinacrine can cause falsely elevated values of **plasma and urine cortisol** values.