Drug Interactions

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

- **ANTACIDS:** May decrease the oral bioavailability of sulfonamides if administered concurrently

Laboratory Considerations

- Sulfonamides may give false-positive results for **urine glucose** determinations when using the Benedict's method.

Doses

- **CATTLE:**

  In calves for labeled indications: 33–49.5 mg/kg PO, or IV twice daily for 1–5 days; suggest initiating therapy with intravenous preparation and then changing to oral if possible (Package insert; *Vetisulid*®—Fort Dodge)

- **SWINE:**

  For labeled indications: 44–77 mg/kg PO per day (divide dose and give twice daily if treating individual animals) for 1–5 days (Package insert; *Vetisulid*®—Fort Dodge)

- **BIRDS:**

  For enteric bacterial infections:

  a) Using the oral powder: Mix 1/4 teaspoonful per liter of water and use as only supply of drinking water for 5–10 days. May be effective for many *E. coli* enteric infections. (Clubb 1986)

  b) Using the oral powder: Mix 3/4 teaspoonsful per 2 quarts of water. Fairly effective for enteric infections, particularly *E. coli*. Reserved for clients who are unable to give other medications by mouth or parenterally. (McDonald 1989)

  c) For pigeons: 1200 mg per gallon of drinking water. Very effective for *E. coli* and it is a good coccidiostat. (Harlin 2006)

Monitoring

- Clinical efficacy
- Adverse effects

Client Information

- To help reduce the possibility of crystalluria occurring, animals should have free access to water; avoid dehydration.

Chemistry/Synonyms

Sulfachlorpyridazine sodium is listed as a short to intermediate-acting, low lipid soluble sulfonamide antibacterial. It is reportedly very soluble in urine at usual pH's.

Sulfachlorpyridazine may also be known as cluricol, sulphachlorpyridazine, or *Vetisulid*®.

Storage/Stability/Compatibility

The injection should be stored at room temperature and protected from light; avoid freezing. The oral suspension should be stored at room temperature; avoid freezing. The oral boluses and powder should be stored at room temperature; avoid excessive heat (above 40°C/104°F).

No information was located regarding the compatibility of sulfachlorpyridazine with other fluids or agents.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Sulfachlorpyridazine Sodium Oral powder: 54 grams per bottle; *Vetisulid*® *Powder* (Fort Dodge); (OTC) Indicated for use in calves under one month of age and swine. Slaughter withdrawal (at labeled doses) = 7 days for cattle and 4 days for swine.

Sulfachlorpyridazine Sodium Oral Suspension: 50 mg/mL in 180 mL bottles; *Vetisulid*® *Oral Suspension* (Fort Dodge); (OTC). Approved for use in swine. Slaughter withdrawal (at labeled doses) = 4 days for swine.

HUMAN-LABELED PRODUCTS: None

Sulfadiazine/Pyrimethamine — See Pyrimethamine/Sulfadiazine

SULFADIAZINE/TRIMETHOPRIM SULFAMETHOXAZOLE/TRIMETHOPRIM

(sul-fa-*dye*-a-zeen; sul-fa-meth-*ox*-a-zole/trye-*meth*-ohe-prim) Co-trimoxazole, Tribrissen®, Bactrim®, Septra®

POTENTIATED SULFONAMIDE ANTIMICROBIAL

Note: In the practice of veterinary medicine in the USA, two separate combinations with trimethoprim are used clinically. There are trimethoprim/sulfadiazine products approved for use in dogs, cats, and horses in both parenteral and oral dosage forms. Many veterinarians also use the human approved, trimethoprim/sulfamethoxazole oral products. In Canada, sulfadoxine is available in combination with trimethoprim for veterinary use.

Prescriber Highlights

- **Potentiated sulfonamide antimicrobial agent**
- **Contraindications: Hypersensitivity to sulfas, thiazides, or sulfonylurea agents; severe renal or hepatic impairment**
- **Caution: Diminished renal or hepatic function, or urinary obstruction or urolithiasis**
- **Adverse Effects: DOGS: Keratoconjunctivitis sicca, hypersensitivity (type 1 or type 3), acute neutrophilic hepatitis with icterus, vomiting, anorexia, diarrhea, fever, hemolytic anemia, urticaria, polyarthritis, facial swelling, polydipsia, crystalluria, hematuria, polyuria, cholestasis, hypothyroidism, anemias, agranulocytosis, idiosyncratic hepatic necrosis in dogs. CATS: Anorexia, crystalluria, hematuria, leukopenias & anemias. HORSES: Transient pruritic (after IV injection). Oral: diarrhea, hypersensitivity reactions & hematologic effects (anemias, thrombocytopenia, or leukopenias**
- **Local injection effects possible (check label for product recommendation for injection technique)**
- **Potentially teratogenic, weigh risk vs. benefit**

Uses/Indications

Although only approved for use in dogs and horses, trimethoprim/sulfadiazine etc. is used in many species to treat infections caused by susceptible organisms. See Dosage section for more information.

Pharmacology/Actions

Alone, sulfonamides are bacteriostatic agents and trimethoprim is bactericidal, but when used in combination, the potentiated sulfas are bactericidal. Potentiated sulfas sequentially inhibit enzymes in the folic acid pathway, inhibiting bacterial thymidine synthesis. The sulfonamide blocks the conversion of para-aminobenzoic acid (PABA) to dihydrofolic acid (DFA), and trimethoprim blocks the

conversion of DFA to tetrahydrofolic acid by inhibiting dihydrofolate reductase.

The *in vitro* optimal ratio for most susceptible bacteria is approximately 1:20 (trimethoprim:sulfa), but synergistic activity can reportedly occur with ratios of 1:1 – 1:40. The serum concentration of the trimethoprim component is considered more important than the sulfa concentration. For most susceptible bacteria, the MIC's for TMP are generally above 0.5 mcg/mL.

The potentiated sulfas have a fairly broad spectrum of activity. Gram-positive bacteria that are generally susceptible include most streptococci, many strains of staphylococcus, and Nocardia. In horses, approximately 30% of strains tested of *Streptococcus zooepidemicus* are resistant to TMP/Sulfa. Many gram-negative organisms of the family Enterobacteriaceae are susceptible to the potentiated sulfas, but not *Pseudomonas aeruginosa*. Some protozoa (*Pneumocystis carinii*, Coccidia, and Toxoplasma) are also inhibited by the combination. Potentiated sulfas reportedly have little activity against most anaerobes, but opinions on this vary.

Resistance will develop more slowly to the combination of drugs than to either one alone. In gram-negative organisms, resistance is usually plasmid-mediated.

Pharmacokinetics

Trimethoprim/sulfa is well absorbed after oral administration, with peak levels occurring about 1 – 4 hours after dosing; the drug is more slowly absorbed after subcutaneous absorption, however. In ruminants, trimethoprim is apparently trapped in the ruminoreticulum after oral administration and undergoes some degradation.

Trimethoprim/sulfa is well distributed in the body. When meninges are inflamed, the drugs enter the CSF in levels of about 50% those found in the serum. Both drugs cross the placenta and are distributed into milk. The volume of distribution for trimethoprim in various species are: 1.49 L/kg (dogs); 0.59 – 1.51 L/kg (horses). The volume of distribution for sulfadiazine in dogs is 1.02 L/kg.

Trimethoprim/sulfa is both renally excreted unchanged via glomerular filtration and tubular secretion and metabolized by the liver. The sulfas are primarily acetylated and conjugated with glucuronic acid and trimethoprim is metabolized to oxide and hydroxylated metabolites. Trimethoprim may be more extensively metabolized in the liver in adult ruminants, than in other species. The serum elimination half-lives for trimethoprim in various species is: 2.5 hours (dogs), 1.91 – 3 hours (horses), 1.5 hours (cattle). The serum elimination half-lives for sulfadiazine in various species is: 9.84 hours (dogs), 2.71 hours (horses), and 2.5 hours (cattle). While trimethoprim is rapidly eliminated from the serum, the drug may persist for a longer period of time in tissues.

Because of the number of variables involved, it is extremely difficult to apply pharmacokinetic values in making dosage recommendations with these combinations. Each drug (trimethoprim and the sulfa) has different pharmacokinetic parameters (absorption, distribution, elimination) in each species. Since different organisms have different MIC values and the optimal ratio of trimethoprim to sulfa differs from organism to organism, this problem is exacerbated.

There is considerable controversy regarding the frequency of administration of these combinations. The veterinary product, trimethoprim/sulfadiazine is labeled for once daily administration in dogs and horses, but many clinicians believe that the drug is more efficacious if given twice daily, regardless of which sulfa is used.

Contraindications/Precautions/Warnings

The manufacturer states that trimethoprim/sulfadiazine should not be used in dogs or horses showing marked liver parenchymal damage, blood dyscrasias, or those with a history of sulfonamide sensitivity. It is not for use in horses (or approved for other animals) intended for food.

This combination should be used with caution in patients with pre-existing hepatic disease.

Because of its potential for crystallization in the urine, it may be wise to avoid the use of sulfadiazine in dogs known to have uroliths, at increased risk for developing uroliths or known to have highly concentrated or acidic urine.

Adverse Effects

Adverse effects noted in dogs include: keratoconjunctivitis sicca (which may be irreversible), acute neutrophilic hepatitis with icterus, vomiting, anorexia, diarrhea, fever, hemolytic anemia, urticaria, polyarthritis, facial swelling, polydipsia, polyuria and cholestasis. Potentiated sulfonamides may cause hypothyroidism in dogs, particularly with extended therapy. Acute hypersensitivity reactions manifesting as Type I (anaphylaxis) or Type III reaction (serum sickness) can be seen. Hypersensitivity reactions appear to be more common in large breed dogs; Doberman Pinschers may possibly be more susceptible to this effect than other breeds. Other hematologic effects (anemias, agranulocytosis) are possible, but fairly rare. TMP/Sulfa has rarely been noted to cause an idiosyncratic, moderate to massive hepatic necrosis. TMP/Sulfa may be a risk factor for developing acute pancreatitis, but cause and effect have not been definitively shown.

Adverse effects noted in cats may include anorexia, leukopenias and anemias.

In horses, transient pruritus has been noted after intravenous injection. Oral therapy has resulted in diarrhea in some horses. Previous administration of potentiated sulfas has been implicated in increasing the mortality rate of associated with severe diarrhea. If the 48% injectable product is injected IM, SC, or extravasates after IV administration, swelling, pain and minor tissue damage may result. Hypersensitivity reactions and hematologic effects (anemias, thrombocytopenia, or leukopenias) may also be seen; long-term therapy should include periodic hematologic monitoring.

Sulfonamides (or their metabolites) can precipitate in the urine, particularly when given at high dosages for prolonged periods. Acidic urine or highly concentrated urine may also contribute to increased risk of crystalluria, hematuria, and renal tubule obstruction.

Reproductive/Nursing Safety

Safety of trimethoprim/sulfa has not been clearly established in pregnant animals. Reports of teratogenicity (cleft palate) have been reported. Studies thus far in male animals have not demonstrated any decreases in reproductive performance. 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.*) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as in class: ***B*** (*Safe for use if used cautiously. Studies in laboratory animals may have uncovered some risk, but these drugs appear to be safe in dogs and cats or these drugs are safe if they are not administered when the animal is near term.*)

Use TMP/sulfa products in nursing animals with caution. TMP-SMZ is not recommended for human use in the nursing period as sulfonamides are excreted in milk and may cause kernicterus. Premature infants and infants with hyperbilirubinemia or G-6-PD deficiency are also at risk for adverse effects.

Overdosage/Acute Toxicity

Manifestations of an acute overdosage can include clinical signs of GI distress (nausea, vomiting, diarrhea), CNS toxicity (depression, headache, and confusion), facial swelling, bone marrow depression and increases in serum aminotransferases. Oral overdoses can be treated by emptying the stomach, (following usual protocols), and initiating symptomatic and supportive therapy. Acidification of the urine may increase the renal elimination of trimethoprim, but could also cause sulfonamide crystalluria, particularly with sulfadiazine containing products. Complete blood counts (and other laboratory parameters) should be monitored as necessary. Bone marrow suppression associated with chronic overdoses may be treated with folinic acid (leucovorin) if severe. Peritoneal dialysis is not effective in removing TMP or sulfas from the circulation.

Drug Interactions

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

- **AMANTADINE:** A human patient developed toxic delirium when receiving amantadine with TMP/sulfa
- **ANTACIDS:** May decrease the bioavailability of sulfonamides if administered concurrently
- **CYCLOSPORINE:** TMP/sulfa may increase the risk of nephrotoxicity
- **DIGOXIN:** TMP/sulfa may increase digoxin levels
- **DIURETICS, THIAZIDE:** May increase risk for thrombocytopenia
- **HYPOGLYCEMIC AGENTS, ORAL:** TMP/sulfa may potentiate effects
- **METHOTREXATE:** TMP/sulfa may displace from plasma proteins and increase risk for toxic effects; it can also interfere with MTX assays (competitive protein binding technique)
- **PHENYTOIN:** TMP/sulfa may increase half-life
- **TRICYCLIC ANTIDEPRESSANTS:** TMP/sulfa may decrease efficacy
- **WARFARIN:** TMP/sulfa may prolong INR/PT

Laboratory Considerations

- When using the Jaffe alkaline picrate reaction assay for **creatinine** determination, trimethoprim/sulfa may cause an overestimation of approximately 10%.
- Sulfonamides may give false-positive results for **urine glucose** determinations when using the Benedict's method.

Doses

Note: There is significant controversy regarding the frequency of dosing these drugs. See the pharmacokinetic section above for more information. Unless otherwise noted, doses are for combined amounts of trimethoprim/sulfa.

- **DOGS:**

  For susceptible infections:

  a) For UTI, pyoderma, soft tissue infections: 30 mg/kg PO q24h (not soft tissue infections) or 15 mg/kg PO q12h for 14 days.

  For chronic pyoderma, acanthamebiasis: 30 mg/kg PO q12h for 21–42 days.

  For systemic infections; bacteremia: 30–45 mg/kg PO q12h for 3–5 days. (Greene, Hartmannn et al. 2006)

  b) For bacterial UTI: 30 mg/kg q12h PO (Bartges 2007)

  c) For protozoal diseases:

  For toxoplasmosis: 15 mg/kg, PO q12h for 28 days.

  For Neospora: 15 mg/kg, PO q12h for 4 weeks. Used concurrently with clindamycin (10 mg/kg q12h for 4 weeks) *or* pyrimethamine (1 mg/kg PO once daily for 4 weeks).

  For *Hepatazoon canis*: 15 mg/kg, PO q12h for 2–4 weeks. Used concurrently with clindamycin (10 mg/kg PO q8h for 2–4 weeks) *and* pyrimethamine (0.25 mg/kg PO once daily for 2–4 weeks) (Lappin 2000)

  d) For coccidiosis: 30 mg/kg PO once daily for 10 days (Matz 1995)

  e) For pneumocystosis (*Pneumocystis carinii*): 15 mg/kg PO q8h or 30 mg/kg PO q12h, both for 3 weeks. May be given with cimetidine and levamisole as potential immune stimulants. (Hawkins 2000)

  f) For *Hepatazoon americanum*: TMP/sulfa (15 mg/kg PO q12h), pyrimethamine (0.25 mg/kg PO q24h), and clindamycin (10 mg/kg q8h). Once remission attained decoquinate (see monograph) can maintain. (Baneth 2007)

  g) For *Hepatazoon americanum*: TMP/sulfa (15 mg/kg PO q12h for 14 days), pyrimethamine (0.25 mg/kg PO q24h for 14 days), and clindamycin (10 mg/kg q8h for 14 days). Once remission attained decoquinate (see monograph) can maintain.

  For neosporosis: pyrimethamine (1 mg/kg PO daily) with TMP/sulfa (15–30 mg/kg PO twice daily. (Blagburn 2005a)

- **CATS:**

  For susceptible infections:

  a) For UTI: 30 mg/kg PO q24h for 7–14 days.

  For UTI, soft tissue infections: 15 mg/kg PO q12h for 7–14 days. (Greene, Hartmannn et al. 2006)

  b) 30 mg/kg q12h (if treating Nocardia, double dose) (Ford and Aronson 1985)

  c) For toxoplasmosis: 15 mg/kg PO q12h for 28 days (Lappin 2000)

  d) For bacterial UTI: 30 mg/kg q12h PO (Bartges 2007)

- **FERRETS:**

  For susceptible infections:

  a) 30 mg/kg PO twice daily (Williams 2000)

  b) For coccidiosis: 30 mg/kg PO once daily for 14 days. (Johnson 2006c)

- **RABBITS, RODENTS, SMALL MAMMALS:**

  a) Rabbits: 15–30 mg/kg, PO q12–24h; 30–48 mg/kg SC q12h. Sulfadiazine has a very short half-life (approx. 1 hour) in rabbits. (Ivey and Morrisey 2000)

  b) Chinchillas, Gerbils, Guinea Pigs, Hamsters, Mice, Rats: 15–30 mg/kg PO q12h; or 30 mg/kg IM q12h (Adamcak and Otten 2000)

  c) Chinchillas: 30 mg/kg PO, SC or IM q12h (Hayes 2000)

- **CATTLE:**

  For susceptible infections:

  a) 44 mg/kg once daily IM or IV using 48% suspension (Upson 1988)

  b) 25 mg/kg, IV or IM q24h (Burrows 1980)

  c) Calves: 48 mg/kg IV or IM q24h (Baggot 1983)

- **HORSES:**

  For susceptible infections:

  a) For respiratory tract infections: 15–30 mg/kg PO q12h. Give 30 minutes prior to feeding hay (grain is OK) (Foreman 1999)

b) Foals: 15 mg/kg IV q12h; 30 mg/kg PO q12h (Brumbaugh 1999)
c) 22 mg/kg IV q24h or 30 mg/kg, PO q24h (Upson 1988)
d) 30 mg/kg PO once daily or 21.3 mg/kg IV once daily (Package inserts; *Tribrissen*®—Coopers)
e) Foals: 15 mg/kg PO or IV twice daily (Furr 1999)
f) For EPM: Sulfadiazine 20 mg/kg (either alone or as a potentiated sulfa) PO once or twice a day with Pyrimethamine (1 mg/kg PO once a day) for 90–120 days (or longer). Monitor: CBC's (Moore 1999)

- **SWINE:**

For susceptible infections:
a) 48 mg/kg, IM q24h (Baggot 1983)

- **BIRDS:**

For susceptible infections:
a) Using TMP/SMX oral suspension (240 mg/5 mL): 2 mL/kg PO twice daily. Good for many gram-positive and negative enteric and respiratory infections, particularly in hand-fed babies. May cause emesis in Macaws. (McDonald 1989)
b) For respiratory and enteric infections in psittacines using the 24% injectable suspension: 0.22 mL/kg IM once to twice daily.

For coccidiosis in toucans and mynahs using TMP/SMX oral suspension (240 mg/5 mL): 2.2 mL/kg once daily for 5 days. May be added to feed.

For respiratory and enteric infections in hand-fed baby psittacines using TMP/SMX oral suspension (240 mg/5 mL): 0.22 mL/30 grams twice daily to three times daily for 5–7 days. (Clubb 1986)
c) Using oral suspension: 50–100 mg/kg (of combined product) PO q12h (Hoeffer 1995)
d) Ratites: For Toxoplasma gondii: 30–50 mg/kg IM twice daily (Jenson 1998)

- **REPTILES:**

For susceptible infections:
a) For most species: 30 mg/kg IM (upper part of body) once daily for 2 treatments, then every other day for 5–12 treatments. May be useful for enteric infections. (Gauvin 1993)
b) For all species: 30 mg/kg IM, first two doses 24 hours apart and then every other day (Jacobson 1999)
c) 15–25 mg/kg/day IM for 7–14 days (Lewbart 2001)

Monitoring

- Clinical efficacy
- Adverse effects; with chronic therapy, periodic complete blood counts should be considered
- Thyroid function tests should be considered (baseline and ongoing) particularly in dogs receiving long-term treatment

Client Information

- If using oral suspension, shake well before using; does not need to be refrigerated
- Animals must be allowed free access to water and must not become dehydrated while on therapy
- If dogs eyes are dry or become irritated contact veterinarian

Chemistry/Synonyms

Trimethoprim occurs as odorless, bitter-tasting, white to cream-colored crystals or crystalline powder. It is very slightly soluble 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.

Sulfamethoxazole occurs as a practically odorless, white to off-white, crystalline powder. Approximately 0.29 mg are soluble in 1 mL of water and 20 mg are soluble in 1 mL of alcohol.

In combination, these products may be known as: Co-trimoxazole, SMX-TMP, TMP-SMX, trimethoprim-sulfamethoxazole, sulfamethoxazole-trimethoprim, sulfadiazine-trimethoprim, trimethoprim-sulfadiazine, TMP-SDZ, SDZ-TMP, Co-trimazine or by their various trade names.

Storage/Stability

Unless otherwise instructed by the manufacturer, trimethoprim/sulfadiazine and co-trimoxazole products should be stored at room temperature (15–30°C) in tight containers.

Dosage Forms/Regulatory Status/Withdrawal Times

VETERINARY-LABELED PRODUCTS:

Trimethoprim (TMP)/Sulfadiazine (SDZ) Oral Paste: Each gram contains 67 mg trimethoprim and 333 mg sulfadiazine. Available in 37.5 gram (total weight) syringes; *Tribrissen® 400 Oral Paste* (Schering-Plough); (Rx). Approved for use in horses not intended for food.

Trimethoprim/Sulfadiazine Sterile Injection: 48% in 100 mL vials: *Di-Biotic® 48%* (Phoenix Pharmaceutical), *Tribrissen® 48% Injection* (Schering-Plough); (Rx) Approved for use in horses not intended for food.

Trimethoprim/Sulfadiazine Powder: 67 mg trimethoprim and 333 mg sulfadiazine per gram: *Tucoprim® Powder* (Pharmacia & Upjohn) in 200 g & 400 g bottles and 2000 g pails, *Uniprim® Powder* (Macleod) in 37.5 g and 1,125 g packets, 200 g jar, and 12 kg box; (Rx). Approved for use in horses not intended for food.

In Canada, trimethoprim and sulfadoxine are available for use in cattle and swine (*Trivetrin*®—Wellcome; *Borgal*®—Hoechst). Slaughter withdrawal = 10 days; milk withdrawal = 96 hours.

HUMAN-LABELED PRODUCTS:

Trimethoprim (alone) Tablets: 100 mg and 200 mg; *Proloprim*® (Glaxo Wellcome); *Trimpex*® (Roche); generic; (Rx)

Trimethoprim 80 mg and Sulfamethoxazole 400 mg Tablets; Trimethoprim 160 mg and Sulfamethoxazole 800 mg Tablets: *Bactrim*®, *Bactrim-DS*® (Roche); *Septra*®, *Septra® DS*, (Glaxo Wellcome); generic; (Rx)

Trimethoprim 8 mg/mL and Sulfamethoxazole 40 mg/mL oral suspension in 20 mL, 100 mL, 150 mL, 200 mL, 473 mL, and 480 mL; *Septra*® (GlaxoWellcome); *Cotrim® Pediatric* (Lemmon), Sulfatrim®, (various); generic; (Rx)

Trimethoprim 16 mg/5 mL (3.2 mg/mL) and Sulfamethoxazole 80 mg/5 mL (16 mg/mL) for injection in 5 mL Carpuject; 80 mg/5 mL (16 mg/mL) trimethoprim and 400 mg/5 mL (80 mg/mL) sulfamethoxazole in 10 mL, 20 mL, 30 mL multi-dose vials and 5 mL vials; *Bactrim® IV* (Roche); *Septra® IV* (Monarch); generic; (Rx)

SULFADIMETHOXINE

(sul-fa-***dye***-meth-***ox***-een) Albon®

SULFONAMIDE ANTIMICROBIAL

Prescriber Highlights

- Sulfonamide antimicrobial agent
- Contraindications: Hypersensitivity to sulfas, thiazides, or sulfonylurea agents; severe renal or hepatic impairment
- Caution: Diminished renal or hepatic function, or urinary obstruction.
- Adverse Effects: Can precipitate in the urine (esp. with high dosages for prolonged periods, acidic urine or highly concentrated urine). DOGS: Keratoconjunctivitis sicca, bone marrow depression, hypersensitivity reactions (rashes, dermatitis), focal retinitis, fever, vomiting & nonseptic polyarthritis possible
- Potentially teratogenic; weigh risk vs. benefit

Uses/Indications

Sulfadimethoxine injection and tablets are approved for use in dogs and cats for respiratory, genitourinary, enteric and soft tissue infections caused by susceptible organisms. Sulfadimethoxine is used in the treatment of coccidiosis in dogs although not approved for this indication.

In horses, sulfadimethoxine injection is approved for the treatment of respiratory infections caused by *Streptococcus equi*.

In cattle, the drug is approved for treating shipping fever complex, calf diphtheria, bacterial pneumonia and foot rot caused by susceptible organisms.

In poultry, sulfadimethoxine is added to drinking water to treat coccidiosis, fowl cholera, and infectious coryza.

Pharmacology/Actions

Sulfonamides are usually bacteriostatic agents when used alone. They are thought to prevent bacterial replication by competing with para-aminobenzoic acid (PABA) in the biosynthesis of tetrahydrofolic acid in the pathway to form folic acid. Only microorganisms that synthesize their own folic acid are affected by sulfas.

Microorganisms that are usually affected by sulfonamides include some gram-positive bacteria, including some strains of streptococci, staphylococcus, *Bacillus anthracis*, *Clostridium tetani*, *C. perfringens*, and many strains of Nocardia. Sulfas also have *in vitro* activity against some gram-negative species, including some strains of Shigella, Salmonella, *E. coli*, Klebsiella, Enterobacter, Pasturella, and Proteus. Sulfas have activity against some rickettsia and protozoa (Toxoplasma, Coccidia). Unfortunately, resistance to sulfas is a progressing phenomenon and many strains of bacteria that were once susceptible to this class of antibacterial are now resistant. The sulfas are less efficacious in pus, necrotic tissue, or in areas with extensive cellular debris.

Pharmacokinetics

In dogs, cats, swine, and sheep, sulfadimethoxine is reportedly readily absorbed and well distributed. Relative volumes of distribution range from 0.17 L/kg in sheep to 0.35 L/kg in cattle and horses. The drug is highly protein bound.

In most species, sulfadimethoxine is acetylated in the liver to acetylsulfadimethoxine and excreted unchanged in the liver. In dogs, the drug is not appreciably hepatically metabolized and renal excretion is the basis for the majority of elimination of the drug. Sulfadimethoxine's long elimination half-lives are a result of its appreciable reabsorption in the renal tubules. Serum half-lives reported in various species are: swine 14 hours; sheep 15 hours; horses 11.3 hours.

Contraindications/Precautions/Warnings

Sulfonamides are contraindicated in patients hypersensitive to them, thiazides, or sulfonylurea agents. They are also considered contraindicated in patients with severe renal or hepatic impairment and should be used with caution in patients with diminished renal or hepatic function, or urinary obstruction.

Oral sulfonamides can depress the normal cellulytic function of the ruminoreticulum, but this effect is generally temporary and the animal adapts.

Adverse Effects

Sulfonamides (or their metabolites) can precipitate in the urine, particularly when given at high dosages for prolonged periods. Acidic urine or highly concentrated urine may also contribute to increased risk of crystalluria, hematuria, and renal tubule obstruction. Different sulfonamides have different solubilities at various pH's. Alkalinization of the urine using sodium bicarbonate may prevent crystalluria, but it also decreases the amount available for tubular reabsorption. Crystalluria can usually be avoided with most of the commercially available sulfonamides by maintaining an adequate urine flow. Normal urine pH in herbivores is usually 8 or more, so crystalluria is not frequently a problem. Sulfonamides can also cause various hypersensitivity reactions or diarrhea by altering the normal gut flora.

Too rapid intravenous injection of the sulfas can cause muscle weakness, blindness, ataxia, and collapse.

In dogs, keratoconjunctivitis sicca, bone marrow depression, hypersensitivity reactions (rashes, dermatitis), focal retinitis, fever, vomiting and nonseptic polyarthritis have been reported with sulfonamides.

Oral sulfonamides can depress the normal cellulytic function of the ruminoreticulum, but this effect is generally temporary and the animal adapts.

Because solutions of sulfonamides are usually alkaline, they can cause tissue irritation and necrosis if injected intramuscularly or subcutaneously.

Reproductive/Nursing Safety

Sulfas cross the placenta and may reach fetal levels of 50% or greater of those found in maternal serum; teratogenicity has been reported in some laboratory animals when given at very high doses. They should be used in pregnant animals only when the benefits clearly outweigh the risks of therapy.

Sulfonamides are distributed into milk.