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.

Overdosage/Acute Toxicity

Acute toxicity secondary to overdoses apparently occurs only rarely in veterinary species. In addition to the adverse effects listed above, CNS stimulation and myelin degeneration have been noted after very high dosages.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving sulfonamides 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

- **DOGS:**

For susceptible infections:

a) 25 mg/kg PO, IV, or IM once daily (Davis 1985), (Kirk 1989)
b) 100 mg/kg PO, IV or IM once daily (Upson 1988)
c) 55 mg/kg PO, or IV, or SC initially, then 27.5 mg/kg once daily thereafter (Package insert; *Albon*®—Roche)

For coccidiosis:

a) 55 mg/kg PO initially on the first day of therapy, then 27.5 mg/kg PO once daily for 9 days (Matz 1995)
b) 50 mg/kg once daily for 10–14 days will eliminate oocyst excretion in most dogs and cats. (Marks 2007c)
c) During the infant period (2–6 weeks): 50 mg/kg PO on the first day followed by a daily dose of 25 mg/kg PO until symptoms regress (Macintire 2004)

- **CATS:**

For susceptible infections:

a) 25 mg/kg PO, IV, or IM once daily (Davis 1985), (Kirk 1989)
b) 100 mg/kg PO, IV or IM once daily (Upson 1988)
c) 55 mg/kg PO, or IV, or SC initially, then 27.5 mg/kg once daily thereafter (Package insert; *Albon*®—Roche)

For coccidiosis:

a) 50 mg/kg once daily for the first day, then 25 mg/kg once daily for 14–20 days. Sulfas are coccidiostatic. It is important that supportive care, including fluids and good nutrition be maintained during therapy. (Cornelius and Roberson 1986)
b) 50 mg/kg once daily for 10–14 days will eliminate oocyst excretion in most dogs and cats. (Marks 2007c)

- **FERRETS:**

For susceptible infections:

a) 25 mg/kg PO, SC or IM once daily (Williams 2000)
b) For coccidiosis: 25 mg/kg PO once daily for 14 days. (Johnson 2006c)

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

a) Rabbits: 10–15 mg/kg PO q12h (Ivey and Morrisey 2000)
b) Rabbits: For coccidiosis: 25 mg/kg PO once daily (Burke 1999)
c) Hedgehogs: 2–20 mg/kg/day IM, SC or PO (Smith 2000)
d) Mice, Rats, Gerbils, Hamsters, Guinea pigs, Chinchillas: As a coccidiostat: 50 mg/kg PO once, then 25 mg/kg PO once daily for 10–20 days *or* 75 mg/kg PO for 7–14 days (Adamcak and Otten 2000)

- **CATTLE:**

For susceptible infections:

a) 110 mg/kg PO or IV once daily (Upson 1988)
b) 55 mg/kg IV initially, then 27.5 mg/kg IV once daily (Baggot 1983)
c) 110 mg/kg, PO q24h (Burrows 1980)
d) 55 mg/kg PO or IV initially, then 27.5 mg/kg q24h (Jenkins 1986)
e) 55 mg/kg IV or PO initially, then 27.5 mg/kg q24h IV or PO for up to 5 days. If using sustained release boluses: 137.5 mg/kg PO every 4 days (Package insert; *Albon*®—Roche)

- **HORSES:**

For susceptible infections:

a) 55 mg/kg, PO or IV q12h (Upson 1988)
b) 55 mg/kg IV or PO initially, then 27.5 mg/kg q24h IV (Package insert; *Albon*®—Roche)

- **REPTILES:**

For susceptible infections:

a) For coccidia: 90 mg/kg PO on day one and then 45 mg/kg PO on 5 successive days; may also be given IM or IV. Maintain adequate hydration. (Lewbart 2001)

Chemistry/Synonyms

A long-acting sulfonamide, sulfadimethoxine occurs as an odorless or almost odorless, creamy white powder. It is very slightly soluble in water and slightly soluble in alcohol.

Sulfadimethoxine may also be known as: solfadimetossina, solfadimetossipirimidina, sulphadimethoxine, *Albon*®, *Amtech*®, *Chemiosalfa*®, *Deltin*®, *Di-Methox*®, *Risulpir*®, *Ritarsulfa*®, *SDM*®, *Sulfadren*®, *Sulfastop*®, or *Sulfasol*®, and *Sulfathox*®.

Storage/Stability

Unless otherwise instructed by the manufacturer, store sulfadimethoxine products at room temperature and protect from light. If crystals form due to exposure to cold temperatures, either warm the vial or store at room temperature for several days to resolubolize the drug; efficacy is not impaired by this process.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Sulfadimethoxine Injection: 400 mg/mL (40%) in 100 mL vials; *Albon® Injection 40%* (Pfizer Animal Health); *Amtech® Sulfadimethoxine Injection 40%* (IV use only in cattle) (Phoenix Scientific), *Di-Methox® Injection 40%* (AgriLabs), generic; (Agripharm, Aspen, Butler, Durvet, Vedco), *SDM® Injection* (Phoenix Pharmaceutical); (Rx) Approved for use in dogs, cats, horses, swine and cattle. Not to be used in horses intended for food or calves to be processed for veal. Slaughter withdrawal (at labeled doses) = 5 days (cattle); milk withdrawal (at labeled doses) = 60 hours.

Sulfadimethoxine Oral Tablets: 125 mg, 250 mg, and 500 mg; *Albon® Tablets* (Pfizer Animal Health); (Rx). Approved for use in dogs and cats.

Sulfadimethoxine Oral Suspension: 50 mg/mL in 2 oz. and 16 oz. Bottles; *Albon®* (Pfizer); (Rx). Approved for use in dogs and cats.

Sulfadimethoxine Oral Boluses: 5 g, and 15 g; *Albon®* (Pfizer); (OTC). Approved for use in cattle. Not to be used in calves to be processed for veal. No withdrawal period has been established for this in preruminating calves. Slaughter withdrawal (at labeled doses) = 7 days (cattle); milk withdrawal (at labeled doses) = 60 hours.

Sulfadimethoxine Oral Boluses Sustained-Release: 12.5 g; *Albon® SR* (Pfizer); (Rx) Approved for use in non-lactating cattle. Slaughter

withdrawal (at labeled doses) = 21 days (cattle), a withdrawal period has not been established for pre-ruminating calves. Not for use in calves intended to be processed for veal.

Sulfadimethoxine Soluble Powder: 94.6 g/packet (for addition to drinking water); *Albon*® (Pfizer), *Di-Methox*® *Soluble Powder* (AgriLabs), generic; (AgriPharm, Aspen, Durvet, Phoenix Scientific, Vedco), *Sulfasol*® (Med-Pharmex); (OTC) Approved for use in dairy calves, dairy heifers, beef cattle, broiler and replacement chickens only, and meat-producing turkeys. Slaughter withdrawal (at labeled doses) = 7 days (cattle); 5 days (poultry—do not use in chickens over 16 weeks old or in turkeys over 24 weeks old).

Sulfadimethoxine 12.5% Concentrated Solution (for addition to drinking water): *Albon*® (Pfizer), *Amtech*® generic; (Phoenix Scientific), *Di-Methox*® *12.5% Oral Solution* (AgriLabs), *SDM*® *Solution* (Phoenix Pharmaceutical), generic; (AgriPharm, Aspen, Butler, Durvet, Vedco), *Sulforal*® (Med-Pharmex); (OTC). Approved for use in chickens, turkeys and cattle. Slaughter withdrawal (at labeled doses) = 7 days (for dairy calves, dairy heifers and beef cattle only. Withdrawal for pre-ruminating calves has not been established) Not to be used in calves to be processed for veal; 5 days (poultry—do not use in chickens over 16 weeks old or in turkeys over 24 weeks old).

HUMAN-LABELED PRODUCTS: None

SULFADIMETHOXINE/ ORMETOPRIM

(or-me-*toe*-prim) Primor®

POTENTIATED SULFONAMIDE ANTIMICROBIAL

Prescriber Highlights

- Potentiated sulfa similar to trimethoprim/sulfa. The following apply to TMP/Sulfa & may correlate to this agent as well:
- Contraindications: Hypersensitive 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
- Potentially teratogenic, weigh risk vs. benefit

Uses/Indications

Sulfadimethoxine/ormetoprim is approved for the treatment of skin and soft tissue infections in dogs caused by susceptible strains of *Staphylococcus aureus* and *E. coli*.

Pharmacology/Actions

Sulfadimethoxine/ormetoprim shares mechanisms of action and probably the bacterial spectrum of activity with trimethoprim/sulfa. Alone, sulfonamides are bacteriostatic agents, but in combination with either ormetoprim or trimethoprim, the potentiated sulfas are bactericidal. Potentiated sulfas sequentially inhibit enzymes in the folic acid pathway, thereby inhibiting bacterial thymidine synthesis. The sulfonamide blocks the conversion of para-aminobenzoic acid (PABA) to dihydrofolic acid (DFA) and ormetoprim blocks the conversion of DFA to tetrahydrofolic acid by inhibiting dihydrofolate reductase.

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. 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

The pharmacokinetics of sulfadimethoxine are outlined in the previous monograph. Pharmacokinetic data for ormetoprim is not available at the time of this writing, but the manufacturer states that therapeutic levels are maintained over 24 hours at recommended doses.

Contraindications/Precautions/Warnings

The manufacturer states that ormetoprim/sulfadimethoxine should not be used in dogs showing marked liver parenchymal damage, blood dyscrasias, or in those with a history of sulfonamide sensitivity.

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

Adverse Effects

This combination would be expected to exhibit an adverse reaction profile in dogs similar to that seen with trimethoprim/sulfa, including: 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. Acute hypersensitivity reactions manifesting as Type I, (anaphylaxis) or Type III reaction (serum sickness) can also 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.

Long-term (8 weeks) therapy at recommended doses with ormetoprim/sulfadimethoxine (27.5 mg/kg once daily) resulted in elevated serum cholesterol, thyroid and liver weights, mild follicular thyroid hyperplasia, and enlarged basophilic cells in the pituitary. The manufacturer states that the principal treatment-related effect of extended or excessive usage is hypothyroidism.

Reproductive/Nursing Safety

Safety of ormetoprim/sulfadimethoxine has not been established in pregnant animals. Reports of teratogenicity (cleft palate) have been reported in some lab animals with trimethoprim/sulfa.

Overdosage/Acute Toxicity

In experimental studies in dogs, doses greater than 80 mg/kg resulted in slight tremors and increased motor activity in some dogs. Higher doses may result in depression, anorexia, or seizures.

It is suggested that very high oral overdoses be handled by emptying the gut using standard precautions and protocols and by treating clinical signs supportively and symptomatically.