

# TUCOPRIM® (trimethoprim and sulfadiazine) Powder

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### Powder

#### For Use in Horses

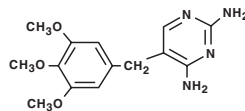
**CAUTION:** Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

#### DESCRIPTION

TUCOPRIM Powder contains 67 mg trimethoprim and 333 mg sulfadiazine per gram.

TUCOPRIM Powder is a combination of trimethoprim and sulfadiazine in the ratio of 1 part to 5 parts by weight, which provides effective antibacterial activity against a wide range of bacterial infections in animals.

The chemical structure of trimethoprim is



The chemical name of trimethoprim is 2,4 diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine.

#### ACTIONS

##### MICROBIOLOGY

Trimethoprim blocks bacterial production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the enzyme dihydrofolate reductase.

Trimethoprim/sulfadiazine thus imposes a sequential double blockade on bacterial metabolism. This deprives bacteria of nucleic acids and proteins essential for survival and multiplication and produces a high level of antibacterial activity that is usually bactericidal.

Although both sulfadiazine and trimethoprim are antifolate, neither affects the folate metabolism of animals. The reasons are that animals do not synthesize folic acid and cannot, therefore, be directly affected by sulfadiazine; and although animals must reduce their dietary folic acid to tetrahydrofolic acid, trimethoprim does not affect this reduction because its affinity for dihydrofolate reductase of mammals is significantly less than for the corresponding bacterial enzyme.

Trimethoprim/sulfadiazine is active against a wide spectrum of bacterial pathogens, both gram-negative and gram-positive. The following *in vitro* data are available, but their clinical significance is unknown. In general, species of the following genera are sensitive to trimethoprim/sulfadiazine:

VERY SENSITIVE	SENSITIVE	MODERATELY SENSITIVE	NOT SENSITIVE
<i>Escherichia</i>	<i>Staphylococcus</i>	<i>Moraxella</i>	<i>Mycobacterium</i>
<i>Streptococcus</i>	<i>Neisseria</i>	<i>Nocardia</i>	<i>Leptospira</i>
<i>Proteus</i>	<i>Klebsiella</i>	<i>Brucella</i>	<i>Pseudomonas</i>
<i>Salmonella</i>	<i>Fusiformis</i>		<i>Erysipelothrix</i>
<i>Pasteurella</i>	<i>Corynebacterium</i>		
<i>Shigella</i>	<i>Clostridium</i>		
<i>Haemophilus</i>	<i>Bordetella</i>		

As a result of the sequential double blockade of the metabolism of susceptible organisms by trimethoprim and sulfadiazine, the minimum inhibitory concentration (MIC) of trimethoprim/sulfadiazine is markedly less than that of either of the components used separately. Many strains of bacteria that are not susceptible to one of the components are susceptible to the combination. A synergistic effect between trimethoprim and sulfadiazine in combination has been shown experimentally both *in vitro* and *in vivo* (in dogs).

Trimethoprim/sulfadiazine is bactericidal against susceptible strains and is often effective against sulfonamide-resistant organisms. *In vitro* sulfadiazine is usually only bacteriostatic.

The precise *in vitro* MIC of the combination varies with the ratio of the drugs present, but action of trimethoprim/sulfadiazine occurs over a wide range of ratios, with an increase in the concentration of one of its components compensating for a decrease in the other. It is usual, however, to determine MICs using a constant ratio of one part trimethoprim in twenty parts of the combination.

The following table shows MICs, using the above ratio of bacteria that were susceptible to both trimethoprim (TMP) and sulfadiazine (SDZ). The organisms are those most commonly involved in conditions for which trimethoprim/sulfadiazine is indicated.

**AVERAGE MINIMUM INHIBITORY CONCENTRATION  
(MIC-MCG/ML)**

Bacteria	TMP	SDZ	TMP/SDZ	
			TMP	SDZ
<i>Escherichia coli</i>	0.31	26.5	0.07	1.31
<i>Proteus species</i>	1.3	24.5	0.15	2.85
<i>Staphylococcus aureus</i>	0.6	17.6	0.13	2.47
<i>Pasteurella species</i>	0.06	20.1	0.03	0.56
<i>Salmonella species</i>	0.15	61.0	0.05	0.95
$\beta$ <i>Streptococcus</i>	0.5	24.5	0.15	2.85

The following table demonstrates the marked effect of the trimethoprim and sulfadiazine combination against sulfadiazine-resistant strains of normally susceptible organisms:

**AVERAGE MINIMUM INHIBITORY CONCENTRATION OF  
SULFADIAZINE-RESISTANT STRAINS (MIC-MCG/ML)**

Bacteria	TMP Alone	SDZ Alone	TMP/SDZ	
			TMP	SDZ
<i>Escherichia coli</i>	0.32	> 245	0.27	5.0
<i>Proteus species</i>	0.66	> 245	0.32	6.2

#### SUSCEPTIBILITY TESTING

In testing susceptibility to trimethoprim/sulfadiazine, it is essential that the medium used does not contain significant amounts of interfering substances that can bypass the metabolic blocking action, e.g., thymidine or thymine.

The standard SxT disc is appropriate for testing by the disc diffusion method.

#### PHARMACOLOGY

Following oral administration, trimethoprim/sulfadiazine is rapidly absorbed and widely distributed throughout body tissues. Concentrations of trimethoprim are usually higher in tissues than in blood. The levels of trimethoprim are high in lung, kidney and liver, as would be expected from its physical properties.

Serum trimethoprim concentrations in horses following oral administration indicate rapid absorption of the drug; peak concentrations occur in 1.5 hours. The mean serum elimination half-life is 2 to 2.5 hours. Sulfadiazine absorption is slower, requiring 2.5 to 6 hours to reach peak concentrations. The mean serum elimination half-life for sulfadiazine is 4 to 5.5 hours.

Usually, the concentration of an antibacterial in the blood and the *in vitro* MIC of the infecting organism indicate an appropriate period between doses of a drug. This does not hold entirely for trimethoprim/sulfadiazine because trimethoprim, in contrast to sulfadiazine, localizes in tissues and therefore its concentration and ratio to sulfadiazine are higher there than in blood.

The following table shows the average concentration of trimethoprim and sulfadiazine, as measured in either serum or plasma, in 24 adult horses observed after a single dose of TUCOPRIM Powder:

(Continued)

**AVERAGE PLASMA CONCENTRATION (mcg/mL)**  
**Trimethoprim (5 mg/kg) Sulfadiazine (25 mg/kg)**

Trimethoprim (5 mg/kg)					Sulfadiazine (25 mg/kg)				
1 hr	3 hr	6 hr	10 hr	24 hr	1 hr	3 hr	6 hr	10 hr	24 hr
0.82	0.69	0.36	0.12	< 0.25	9.9	18.8	17.3	9.0	1.6

Excretion of trimethoprim/sulfadiazine is chiefly by the kidneys, by both glomerular filtration and tubular secretion. Urine concentrations of both trimethoprim and sulfadiazine are severalfold higher than blood concentrations. Neither trimethoprim nor sulfadiazine interferes with the excretion pattern of the other.

**INDICATIONS AND USAGE**

Trimethoprim/sulfadiazine is indicated in horses where potent systemic antibacterial action against sensitive organisms is required. Trimethoprim/sulfadiazine is indicated where control of bacterial infections is required during treatment of

- Acute strangles
- Acute urogenital infections
- Respiratory tract infections
- Wound infections and abscesses

Trimethoprim/sulfadiazine is well tolerated by foals.

**CONTRAINDICATIONS**

Trimethoprim/sulfadiazine should not be used in horses showing marked liver parenchymal damage, blood dyscrasias or in those with a history of sulfonamide sensitivity.

**WARNINGS**

**NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.**

Not for use in horses intended for food.

**PRECAUTION**

Water should be readily available to horses receiving sulfonamide therapy.

**ADVERSE REACTIONS**

No adverse reactions of consequence have been noted following administration of trimethoprim/sulfadiazine. During clinical trials, one case of anorexia and one case of loose feces following treatment with the drug were reported.

Individual animal hypersensitivity may result in local or generalized reactions, sometimes fatal. Anaphylactoid reactions, although rare, may also occur. Antidote: Epinephrine.

**TOXICITY AND SIDE EFFECTS**

Toxicity is low. The acute toxicity (LD50) of trimethoprim/sulfadiazine is more than 5 g/kg orally in rats and mice. No significant changes were recorded in rats given doses of 600 mg/kg per day for 90 days.

Horses treated intravenously with trimethoprim/sulfadiazine 48% Injection have tolerated up to five times the recommended daily dose for seven days or on the recommended daily dose for 21 consecutive days without clinical effects or histopathological changes.

Lengthening of clotting time was seen in some of the horses on high or prolonged dosing in one of two trials. The effect, which may have been related to a resolving infection, was not seen in a second similar trial.

Slight to moderate reductions in hematopoietic activity following high, prolonged dosage in several species have been recorded. This is usually reversible by folic acid (leucovorin) administration or by stopping the drug. During long-term treatment of horses, periodic platelet counts and white and red blood cell counts are advisable.

In rare instances, horses have developed diarrhea during trimethoprim/sulfadiazine treatment. If fecal consistency changes during trimethoprim/sulfadiazine therapy, discontinue treatment immediately and institute appropriate symptomatic measures.

**TERATOLOGY**

The effect of trimethoprim/sulfadiazine on pregnancy has not been determined. Studies to date show there is no detrimental effect on stallion spermatogenesis with or following the recommended dose of trimethoprim/ sulfadiazine.

**DOSAGE AND ADMINISTRATION**

The recommended dose is 3.75 grams TUCOPRIM Powder per 50 kg (110 lb) body weight per day. Each level, loose-filled scoop contains approximately 15 grams, which is sufficient to treat 200 kg (440 lb) of body weight. Since product contents may settle, gentle agitation during scooping is recommended. Administer orally once a day in a small amount of palatable feed.

The usual course of treatment is a single, daily dose for five to seven days. Continue acute infection therapy for two or three days after clinical signs have subsided. If no improvement of acute infections is seen in three to five days, re-evaluate diagnosis.

Trimethoprim/sulfadiazine may be used alone or in conjunction with intravenous dosing. Following treatment with trimethoprim/sulfadiazine 48% Injection, therapy can be maintained using oral powder.

A complete blood count should be done periodically in patients receiving trimethoprim/sulfadiazine for prolonged periods. If significant reduction in the count of any formed blood element is noted, treatment with trimethoprim/sulfadiazine should be discontinued.

**STORAGE CONDITIONS**

Store at or below 30°C.

**HOW SUPPLIED**

TUCOPRIM Powder is available in the following package sizes:

- 200 gram bottle
- 400 gram bottle
- 2000 gram pails

ANADA #200-244, Approved by FDA

Made in the United Kingdom  
Distributed by Pharmacia & Upjohn Company  
Division of Pfizer Inc,  
New York, NY 10017

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