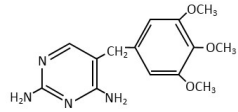
UNIPRIM® POWDER FOR HORSES
(trimethoprim and sulfadiazine)

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

DESCRIPTION: UNIPRIM POWDER FOR HORSES contains 67 mg trimethoprim and 333 mg sulfadiazine per gram.

UNIPRIM POWDER FOR HORSES 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.

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.

Sulfadiazine, in common with other sulfonamides, inhibits bacterial synthesis of dihydrofolic acid by competing with *para*-aminobenzoic acid.

Trimethoprim and 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 which is usually bactericidal.

Although both sulfadiazine and trimethoprim are antifolate, neither affects the folate metabolism of animals. The reasons are: 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 and 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 and sulfadiazine:

Very Sensitive	**Sensitive**	**Moderately Sensitive**	**Not Sensitive**
Escherichia	*Staphylococcus*	*Moraxella*	*Mycobacterium*
Streptococcus	*Neisseria*	*Nocardia*	*Leptospira*
Proteus	*Klebsiella*	*Brucella*	*Pseudomonas*
Salmonella	*Fusiformis*		*Erysipelothrix*
Pasteurella	*Corynebacterium*		
Shigella	*Clostridium*		
Haemophilus	*Bordetella*		

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 and 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 trimethoprim and sulfadiazine. A synergistic effect between trimethoprim and sulfadiazine in combination has been shown experimentally both *in vitro* and *in vivo* (in dogs).

Trimethoprim and 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 and 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 1 part trimethoprim in 20 parts of the combination.

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

AVERAGE MINIMUM INHIBITORY CONCENTRATION (MIC-mcg/mL)				
Bacteria	TMP Alone	SDZ Alone	TMP/SDZ	
			TMP	SDZ
Escherichia coli	0.31	26.5	0.07	1.31
Proteus species	1.30	24.5	0.15	2.85
Staphylococcus aureus	0.60	17.6	0.13	2.47
Pasteurella species	0.06	20.1	0.03	0.56
Salmonella species	0.15	61.0	0.05	0.95
ß Streptococcus	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
Escherichia coli	0.32	>245	0.27	5.0
Proteus species	0.66	>245	0.32	6.2

Susceptibility Testing: In testing susceptibility to trimethoprim and sulfadiazine, it is essential that the medium used does not contain significant amounts of interfering substances which 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 and sulfadiazine are 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 lungs, 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 about 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 and sulfadiazine because trimethoprim, in contrast to sulfadiazine, localizes in tissues and therefore its concentration and ratio to sulfadiazine are higher there than in blood.

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The following table shows the average concentration of trimethoprim and sulfadiazine, as measured in either serum or plasma, in twenty-four adult horses observed after a single dose of UNIPRIM POWDER FOR HORSES:

AVERAGE SERUM/PLASMA CONCENTRATION (mcg/mL)									
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	<0.025	9.9	18.8	17.3	9.0	1.6

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

INDICATIONS AND USAGE: UNIPRIM POWDER FOR HORSES is indicated in horses where potent systemic antibacterial action against sensitive organisms is required. UNIPRIM POWDER FOR HORSES is indicated where control of bacterial infections is required during treatment of:

Acute Strangles
Respiratory Tract Infections
Acute Urogenital Infections
Wound Infections and Abscesses

UNIPRIM POWDER FOR HORSES is well tolerated by foals.

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

WARNING: Do not use in horses intended for human consumption. Keep UNIPRIM POWDER FOR HORSES in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

ADVERSE REACTIONS: 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.

To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Neogen Corporation at 859-254-1221 or neogen.com.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

Post Approval Experience: Horses have developed diarrhea during trimethoprim and sulfadiazine treatment, which could be fatal. If fecal consistency changes during trimethoprim and sulfadiazine therapy, discontinue treatment immediately and contact your veterinarian.

PRECAUTION: Water should be readily available to horses receiving sulfonamide therapy.

ANIMAL SAFETY: Toxicity is low. The acute toxicity (LD_{50}) of trimethoprim and 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 and sulfadiazine 48% injection have tolerated up to five times the recommended daily dose for 7 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 folinic 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.

TERATOLOGY: The effect of trimethoprim and 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 and sulfadiazine.

DOSAGE AND ADMINISTRATION: The recommended dosage is 3.75 g UNIPRIM POWDER FOR HORSES per 110 lbs (50 kg) body weight per day. Administer UNIPRIM POWDER FOR HORSES orally once a day in a small amount of palatable feed.

Dose Instructions: One **37.5 g** packet is sufficient to treat 1100 lbs (500 kg) of body weight. For the **200 g**, **400 g**, and **1200 g** jars, and **2000 g** pail, two level, loose-filled, 32 cc scoops contain 37.5 g, sufficient to treat 1100 lbs (500 kg) of body weight. Since product contents may settle, gentle agitation during scooping is recommended.

The usual course of treatment is a single, daily dose for 5 to 7 days.

Continue acute infection therapy for 2 or 3 days after clinical signs have subsided.

If no improvement of acute infections is seen in 3 to 5 days, reevaluate the diagnosis.

UNIPRIM POWDER FOR HORSES may be used alone or in conjunction with intravenous dosing. Following treatment with trimethoprim and sulfadiazine 48% injection, therapy can be maintained using oral Powder.

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

STORAGE: Store at or below 25°C (77°F)

HOW SUPPLIED: UNIPRIM POWDER FOR HORSES is available in 37.5 g packets, 200 g jars, 400 g jars, and 2000 g pails. Apple Flavored UNIPRIM POWDER FOR HORSES is available in 37.5 g packets, 200 g jars, 400 g jars, 1200 g jars, and 2000 g pails.

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