

Date of Approval: APR 25 2006

**FREEDOM OF INFORMATION SUMMARY**

NADA 131-918

TRIBRISSEN 400 Oral Paste

trimethoprim/sulfadiazine

For control of bacterial infections during treatment of acute strangles, respiratory tract infections, acute urogenital infections, wound infections, and abscesses.

Sponsored by:

Schering-Plough Animal Health Corp.  
556 Morris Ave.  
Summit, NJ 07901

NADA 131.918

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***1. GENERAL INFORMATION:***

- a. File Number: NADA 131-918
- b. Sponsor: Schering-Plough Animal Health Corp.  
556 Morris Ave.  
Summit, NJ 07901
- Drug Labeler Code: 000061
- c. Established Name: trimethoprim/sulfadiazine
- d. Proprietary Name: TRIBRISSEN 400 Oral Paste
- e. Dosage Form: Paste
- f. How Supplied: DIAL-A-DOSE syringe
- g. How Dispensed: Rx
- h. Amount of Active Ingredients: Each gram contains 67 mg trimethoprim and 333 mg sulfadiazine
- i. Route of Administration: Oral
- j. Species/Class: Horses
- k. Recommended Dosage: 3.75 g per 110 lbs (50 kg) body weight once daily given orally.
- l. Pharmacological Category: Antibacterial
- m. Indications: For the control of bacterial infections during treatment of acute strangles, respiratory tract infections, acute urogenital infections, wound infections, and abscesses.
- n. Effect of Supplement: This is a regulatory supplement requesting changes recommended by the Division of Surveillance and ONADE. The labeling supplement adds post-approval experience information, revises the warning statement, and updates the label format.

**2. EFFECTIVENESS:**

- a. **Dosage Characterization:** New information was not required for this supplement.
- b. **Substantial Evidence:** New information was not required for this supplement.

**3. TARGET ANIMAL SAFETY:**

The following Post Approval Experience was added to the label: Horses have developed diarrhea during TRIBRISSEN 400 Oral Paste treatment, which could be fatal. If fecal consistency changes during TRIBRISSEN 400 Oral Paste therapy, discontinue treatment immediately and contact your veterinarian.

**4. HUMAN SAFETY:**

This drug is intended for use in horses, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

Human Warnings are provided on the product label as follows: "Keep out of reach of children. Do not use in horses intended for human consumption."

**5. AGENCY CONCLUSIONS:**

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that TRIBRISSEN 400 Oral Paste when used under the labeled conditions of use is safe and effective for the control of bacterial infections during treatment of acute strangles, respiratory tract infections, acute urogenital infections, wound infections, and abscesses.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to diagnose and treat bacterial infections in horses.

This approval for does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

According to the Center's supplemental approval policy (21 CFR 514.106), this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

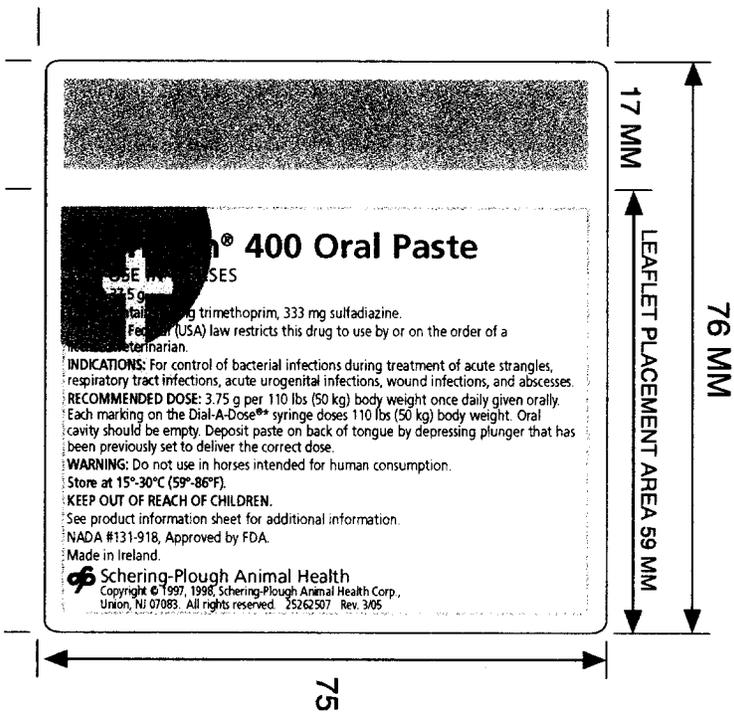
There were no patents submitted with this application.

**6. ATTACHMENTS:**

Facsimile labeling is attached as indicated below:

Carton Front Panel

Package Insert



NADA #131-918, Approved by FDA.

PRODUCT  
INFORMATION

## Tribrissen® 400 Oral Paste

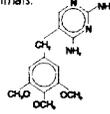
FOR USE IN HORSES

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

**DESCRIPTION:** TRIBRISSEN 400 Oral Paste contains 67 mg trimethoprim and 333 mg sulfadiazine per gram.

TRIBRISSEN Oral Paste 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.

TRIBRISSEN Oral Paste thus imposes a sequential double blockade on bacterial metabolism. This deprives bacteria of nucleic acids and proteins essential for survival and multi-

plication, 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.

TRIBRISSEN Oral Paste 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 TRIBRISSEN Oral Paste:

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 TRIBRISSEN Oral Paste 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 TRIBRISSEN Oral Paste.

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

TRIBRISSEN Oral Paste 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 TRIBRISSEN Oral Paste 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 TRIBRISSEN Oral Paste is indicated:

Bacteria	AVERAGE MINIMUM INHIBITORY CONCENTRATION (MIC-mcg/mL)			
	TMP Alone	SDZ Alone	TMP/SDZ	
			TMP	SDZ
<i>Escherichia coli</i>	0.31	26.5	0.07	1.31
<i>Proteus</i> species	1.3	24.5	0.15	2.85
<i>Staphylococcus aureus</i>	0.6	17.6	0.13	2.47
<i>Pasteurella</i> species	0.06	20.1	0.03	0.56
<i>Salmonella</i> species	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:

Bacteria	AVERAGE MINIMUM INHIBITORY CONCENTRATION OF SULFADIAZINE-RESISTANT STRAINS (MIC-mcg/mL)			
	TMP Alone	SDZ Alone	TMP/SDZ	
			TMP	SDZ
<i>Escherichia coli</i>	0.32	>245	0.27	5.0
<i>Proteus</i> species	0.66	>245	0.32	6.2

**Susceptibility Testing:** In testing susceptibility to TRIBRISSEN Oral Paste, it is essential that the medium used does not contain significant amounts of interfering substances which can bypass the metabolic blocking action, eg, thymidine or thymine.

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

**Pharmacology:** Following oral administration, TRIBRISSEN Oral Paste 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 the 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 2 to 3 hours. The mean serum elimination half-life is 2 to 3 hours. Sulfadiazine absorption is slower, requiring 3 to 6 hours to reach peak concentrations. The mean serum elimination half-life of sulfadiazine is about 7 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 TRIBRISSEN Oral Paste 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 serum concentration of trimethoprim and sulfadiazine in 11 adult horses on Day 3 of three consecutive daily doses of TRIBRISSEN 400 Oral Paste:

AVERAGE SERUM 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	
0.71	0.95	0.37	0.04	<0.04	8.0	15.8	9.9	5.6	0.6	

Excretion of TRIBRISSEN Oral Paste 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:** TRIBRISSEN 400 Oral Paste is indicated in horses where potent systemic antibacterial action against sensitive organisms is required. TRIBRISSEN 400 Oral Paste is indicated where control of bacterial infections is required during treatment of:

Acute Strangles  
Respiratory Tract Infections

Acute Urogenital Infections  
Wound Infections and Abscesses

TRIBRISSEN Oral Paste is well tolerated by foals.

**CONTRAINDICATIONS:** TRIBRISSEN Oral Paste 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.

**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.

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

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

**ANIMAL SAFETY:** Toxicity is low. The acute toxicity (LD<sub>50</sub>) of TRIBRISSEN Oral Paste 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 TRIBRISSEN 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 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.

**TERATOLOGY:** The effect of TRIBRISSEN 400 Oral Paste 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 TRIBRISSEN 400 Oral Paste.

**DOSAGE AND ADMINISTRATION:** The recommended dose is 3.75 g TRIBRISSEN 400 Oral Paste per 110 lbs (50 kg) body weight per day. Administer orally once a day by means of the Dial-A-Dose\*\* syringe. Each marking on the syringe doses 110 lbs (50 kg) body weight. When administering TRIBRISSEN 400 Oral Paste, the oral cavity should be empty. Deposit paste on back of tongue by depressing plunger that has been previously set to deliver the correct dose.

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.

TRIBRISSEN 400 Oral Paste may be used alone or in conjunction with intravenous dosing. Following treatment with TRIBRISSEN 48% Injection, therapy can be maintained using oral paste.

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

**STORAGE:** Store at 15°-30°C (59°-86°F).

**HOW SUPPLIED:** TRIBRISSEN 400 Oral Paste is available in 37.5 g Dial-A-Dose\*\* syringes.

\*Trademark: Plas-Pak Industries, Inc.

## TRIBRISSEN® 400 Oral Paste

### USE IN HORSES

37.5 g of paste containing trimethoprim, 333 mg sulfadiazine.  
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

**INDICATIONS:** For control of bacterial infections during treatment of acute strangles, respiratory tract infections, acute urogenital infections, wound infections, and abscesses.

**RECOMMENDED DOSE:** 3.75 g per 110 lbs (50 kg) body weight once daily given orally. Each marking on the Dial-A-Dose\*\* syringe doses 110 lbs (50 kg) body weight. Oral cavity should be empty. Deposit paste on back of tongue by depressing plunger that has been previously set to deliver the correct dose.

**WARNING:** Do not use in horses intended for human consumption.

Store at 15°-30°C (59°-86°F).

**KEEP OUT OF REACH OF CHILDREN.**

See product information sheet for additional information.

NADA #131-918, Approved by FDA.

Made in Ireland.

 Schering-Plough Animal Health

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