

Pharmaceutical Solutions, Inc.

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Northfield, MN 55057
800-223-1741
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2832 02 FEB 26 02 58

February 25, 2002

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Subject: ANADA Suitability Petition; No Data
Reference: JINAD 10891 R0000

Dear Sir:

The undersigned requests permission to file an ANADA for a generic new animal drug with a different dosage form, method of administration, and strength than the pioneer product.

1 Identity of Petitioner

The petitioner is Pharmaceutical Solutions, Inc., a Minnesota corporation, with its principal offices located at 1196 S. Highway 3, Northfield, Minnesota 55057. The relevant statutory section is section 512(n)(3) of the Federal Food, Drug, and Cosmetic Act.

2 Action Requested

The petitioner requests permission to file an ANADA for a generic version of trimethoprim and sulfadiazine combination for use in horses. The pioneer product is trimethoprim and sulfadiazine oral paste (Tribrissen® 400 Oral Paste), Schering-Plough Animal Health Corporation, NADA 131-918. The proposed product will be the same as the pioneer product except for the dosage form, the method of administration, and the strength.

The proposed product is a liquid (trimethoprim suspension/sulfadiazine solution) to be administered by stomach tube whereas the pioneer product is a paste administered by placing it on the back of the animal's tongue.

The proposed product contains the same active ingredients as the pioneer product in the same weight ratio (5:1, sulfadiazine:trimethoprim) but in different concentrations. The proposed product will be prepared using sodium sulfadiazine powder whereas the pioneer contains sulfadiazine. The sulfadiazine active ingredient is considered to be the same as that of the pioneer since at the pH of the product in solution (pH > 10.0) sodium sulfadiazine will be essentially completely ionized. The pioneer product contains 67 mg trimethoprim and 333 mg

02P-0084

CPI

sulfadiazine per gram of paste. The proposed product will contain 56 mg trimethoprim and 280 mg sulfadiazine per gram of liquid (suspension).

The recommended dose for the pioneer product is 3.75 grams oral paste per 110 lb. (50 kg) body weight. The pioneer product dose is measured by volume using a pre-filled syringe calibrated to body weight. The recommended dose for the proposed product will be 3.75 mL of liquid (suspension) per 110 lb. (50 kg) body weight. At the specific gravity of the proposed product (1.19 g/mL), a volume measure of 3.75 mL of liquid (suspension) will contain the same amount of active ingredients in the same 5:1 weight ratio (sulfadiazine:trimethoprim) as will 3.75 grams of the pioneer product.

The conditions, indications, and limitations of use of the proposed product are the same as the pioneer product. A draft package insert for the proposed product is included in this submission (see below).

Information to show bioequivalence between the proposed product and the pioneer product will be included in the ANADA.

3. Statement of Grounds

The proposed product has the advantage that it will be given by stomach tube. Thus, the proposed product would be expected to improve compliance with prescribed treatment and in so doing improve treatment results in the horse. The expected benefits to compliance and to treatment results justify the proposed variation from the pioneer drug product.

4. Environmental Impact

The proposed product will be marketed under the same conditions of approval as the pioneer product. Therefore, a categorical exclusion from the requirement for an environmental assessment is requested under 21 CFR 25.33(a)(1).

5. Economic Impact

A statement of economic impact will be provided upon request.

6. Certification

A signed statement is attached certifying that this petition contains all information upon which the petition relies and that the undersigned is unaware of any information which is unfavorable to the petition (Attachment A).

7. Additional Information

- 7.1 Approved labeling for the pioneer product that is the basis of this petition, Tribriksen® 400 Oral Paste, is provided (Attachment B).
- 7.2 A draft package insert for the proposed product, Trimethoprim and Sulfadiazine Oral Liquid (Suspension), is provided (Attachment C). Specific differences in the

package inserts of the proposed product and the pioneer product are identified and discussed below.

Identification and Discussion of Labeling Differences for the Proposed Product

- a. Tradename is different.
- b. Dosage Form is different.
- c. Active Ingredients are the same. Strength of both active ingredients is different. The pioneer product contains 67 mg trimethoprim and 333 mg sulfadiazine per gram of oral paste. The proposed product will contain 56 mg trimethoprim and 280 mg sulfadiazine per gram of liquid suspension. The ratio of 1 part trimethoprim to 5 parts sulfadiazine by weight in the proposed product will be the same as for the pioneer product
- d. Indications are the same.
- e. Pharmacology knowledge is the same. This information is presented under the headings "Description" and "Actions" in the pioneer product insert.
- f. Dosage is the same. Since the proposed product is a liquid (suspension), dosage will be changed to a volume measurement instead of the weight measurement described for the pioneer product. Administration of the proposed generic product is by stomach tube.
- g. Contraindications are the same.
- h. Precautions are the same.
- i. Cautions are the same.
- j. Warnings are the same.
- k. Toxicology is the same.
- l. Teratology is the same.
- m. Adverse Reactions is the same.
- n. Antidote is the same.
- o. Presentation is different.

Thank you for your consideration of this petition. If any questions arise regarding this petition, please contact the undersigned by telephone at 800-223-1741.

Respectfully,

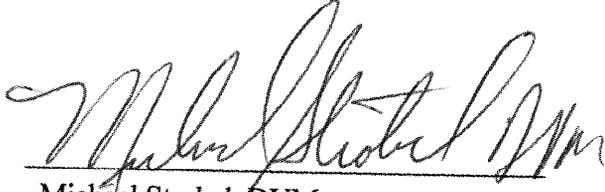


Michael Strobel, DVM
President

Attachment A: Certification

Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information on which the petition relies. The undersigned knows of no information that is unfavorable to the petition.



Michael Strobel, DVM
President
Pharmaceutical Solutions, Inc.
1196 S. Highway 3
Northfield, MN 55057
800-223-1741

2/25/02

Date

Attachment B: Labeling for Pioneer Product, Tribressin® 400 Oral Paste

Source: Commercial Product

Transcription of Approved Pioneer Product Label

Barcode

NDC 0061-5069-01

N
3 0061-5069-01 1

Store at 15°-30° C (59°-86° F).
See package insert for additional information.

** Plas-Pak Industries, Inc.

Schering-Plough
Animal Health Corp.
Union, NJ 07083
Made in Ireland

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: Not for use in horses intended for food.

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

KEEP OUT OF REACH OF CHILDREN

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Schering-Plough Animal Health Corp.
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Tribrissen® 400
Oral Paste
FOR HORSES

Net wt. 37.5 g
Each g contains: 67 mg Trimethoprim
333 mg Sulfadiazine

LOT 018421

NADA #131-918, Approved by FDA.

EXP 07/2004

Schering-Plough Animal Health

Tribrissen® 400 Oral Paste

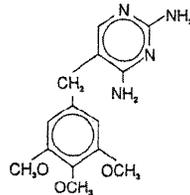
For Use in Horses

NADA #141-0918 Approved by FDA.

DESCRIPTION:

Tribrissen 400 Oral Paste contains 67 mg trimethoprim and 333 mg sulfadiazine per gram. Tribrissen 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 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.

Tribrissen 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:

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

Tribrissen 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 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 which were susceptible to both trimethoprim (TMP) and sulfadiazine (SDZ). The organisms are those most commonly involved in conditions for which Tribrissen 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
β <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

TRIBRISSEN® 400 ORAL PASTE FOR USE IN HORSES

Susceptibility Testing: In testing susceptibility to Tribriszen, 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, Tribriszen 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 2-3 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 for 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 Tribriszen 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 eleven adult horses on day three of three consecutive daily doses of Tribriszen 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 Tribriszen 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:

Tribriszen 400 Oral Paste is indicated in horses where potent systemic antibacterial action against sensitive organisms is required. Tribriszen 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

Tribriszen is well tolerated by foals.

CONTRAINDICATIONS:

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

WARNING:

Not for use in horses intended for food.

ADVERSE REACTIONS:

No adverse reactions of consequence have been noted following administration of Tribriszen 400 Oral Paste. 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.

PRECAUTIONS:

Water should be readily available to horses receiving sulfonamide therapy.

TOXICITY AND SIDE EFFECTS:

Toxicity is low. The acute toxicity (LD₅₀) of Tribriszen 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 Tribriszen 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 Tribriszen treatment. If fecal consistency changes during Tribriszen therapy, discontinue treatment immediately and institute appropriate symptomatic measures.

TERATOLOGY:

The effect of Tribriszen 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 Tribriszen 400 Oral Paste.

DOSAGE AND ADMINISTRATION:

The recommended dose is 3.75 g Tribriszen 400 Oral Paste per 110 lb. (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 lb. (50 kg) body weight. When administering Tribriszen 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 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.

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

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

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

HOW SUPPLIED:

Tribriszen 400 Oral Paste is available in 37.5 g Dial-A-Dose*** syringes.

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

*** Trademark: Plas-Pak Industries, Inc.

Schering-Plough Animal Health Corp.
Union, NJ 07083
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Made in Ireland

20776404 Rev. 10/97

**Attachment C: Draft Package Insert
for Trimethoprim and Sulfadiazine Oral Liquid (Suspension)**

TRADENAME ORAL LIQUID (SUSPENSION)

Rx

Pharmaceutical Solutions

Potentiated Sulfa

ANADA No.: XXX-XXX

Active Ingredients: TRADENAME Oral Liquid (Suspension) contains 56 mg trimethoprim and 280 mg sulfadiazine per gram of liquid (suspension).

Indications: 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, respiratory tract infections, acute urogenital infections, and wound infections and abscesses.

Trimethoprim/sulfadiazine is well tolerated by foals.

Pharmacology: TRADENAME Oral Liquid (Suspension) 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.

[chemical structure of trimethoprim will be inserted here]

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/sulfadiazine thus imposes a sequential double blockade of 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.

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Trimethoprim/sulfadiazine is active against a wide spectrum of bacterial pathogens, both gram-positive and gram-negative. 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: *Escherichia*, *Streptococcus*, *Proteus*, *Salmonella*, *Pasteurella*, *Shigella*, *Haemophilus*.

Sensitive: *Staphylococcus*, *Neisseria*, *Klebsiella*, *Fusiformis*, *Corynebacterium*, *Clostridium*, *Bordetella*.

Moderately Sensitive: *Moraxella*, *Nocardia*, *Brucella*.

Not Sensitive: *Mycobacterium*, *Leptospira*, *Pseudomonas*, *Erysipelothrix*.

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 trimethoprim/sulfadiazine. 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 MIC's using a constant ratio of one part trimethoprim in twenty parts of the combination.

The following table shows MIC's, 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/sulfadiazine is indicated.

Average Minimum Inhibitory Concentration (MIC- μ g/mL)

Bacteria	TMP Alone	SDZ Alone	TMP/SDZ	
			TMP	SDZ
<i>Escherichia coli</i>	0.31	26.5	0.07	1.31
<i>Proteus</i> species	1.30	24.5	0.15	2.85
<i>Staphylococcus aureus</i>	0.60	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
□ <i>Streptococcus</i>	0.50	24.5	0.15	2.85

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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- $\mu\text{g}/\text{mL}$):

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 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.

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 [value will be inserted¹] hours. The mean serum elimination half-life is [value will be inserted] hours. Sulfadiazine absorption is slower requiring [value will be inserted] hours to reach peak concentrations. The mean serum elimination half-life for sulfadiazine is about [value will be inserted] 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 will be inserted], in [number to be inserted] adult horses observed after a single dose of Tradename Oral Liquid (Suspension).

[table of drug concentrations at 1, 3, 6, 10, and 24 hours after dose will be inserted here]

Excretion of trimethoprim/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.

¹ Values for time of peak drug concentrations and elimination half live of the proposed product will be determined via the bioequivalence study.

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Dosage and Administration: The recommended dose is 3.75 mL trimethoprim/sulfadiazine oral liquid (suspension) per 110 lb (50 kg) body weight per day. Administer once a day by stomach tube. Trimethoprim/sulfadiazine oral liquid (suspension) should be shaken before use.

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 the diagnosis.

Trimethoprim/sulfadiazine oral liquid (suspension) may be used alone or in conjunction with intravenous dosing. Following treatment with trimethoprim/sulfadiazine 48% injection, therapy can be maintained using oral liquid (suspension).

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.

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.

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

Warning: Not for use in horses intended for food.

Toxicology: 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 21 consecutive days without clinical effects or histopathological changes.

Lengthening of clotting time was seen in some 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.

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

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. Anaphylactoid reactions, although rare, may also occur. **Antidote:** Epinephrine.

Storage: Store at [temperature range will be inserted here].

Presentation: TRADENAME Oral Liquid (Suspension) is available in [size and type of marketing container will be added here].

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

24

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FedEx USA Airbill FedEx Tracking Number 822746328097

SNA21

Form I.E. No.

0215

1 From This portion can be removed for Recipient's records
Date _____ FedEx Tracking Number **822746328097**

Sender's Name **Michael Strubel DVM** Phone **800 223-1741**

Company **CANNON VALLEY VETERINARY CLINI**

Address **1200 HIGHWAY 3 S**

City **NORTHFIELD** State **MIN** ZIP **55057**

2 Your Internal Billing Reference

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Company **FOOD & Drug Administration Room 1061**

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4a Express Package Service *Packages up to 150 lbs.*
 FedEx Priority Overnight Next business morning FedEx Standard Overnight Next business afternoon FedEx First Overnight Earliest next business morning delivery to select locations

FedEx 2Day* Second business day FedEx Express Saver* Third business day * FedEx Envelope/Letter Rate not available. Minimum charge: One-pound rate.

4b Express Freight Service *Packages over 150 lbs.*
 FedEx 1Day Freight* Next business day FedEx 2Day Freight Second business day FedEx 3Day Freight Third business day

* Call for Confirmation. * Declared value limit \$500

5 Packaging
 FedEx Envelope/Letter* FedEx Pak* Other Pkg. Includes FedEx Box, FedEx Tube, and customer pkg.

6 Special Handling
 SATURDAY Delivery Available for FedEx Priority Overnight and FedEx 2Day to select ZIP codes SUNDAY Delivery Available for FedEx Priority Overnight to select ZIP codes HOLD Weekday at FedEx Location Not available with FedEx First Overnight HOLD Saturday at FedEx Location Available for FedEx Priority Overnight and FedEx 2Day to select locations

Does this shipment contain dangerous goods?
 No Yes As per attached Shipper's Declaration Yes Shipper's Declaration not required Dry Ice Dry Ice, 3, UN 1845 Cargo Aircraft Only

7 Payment Bill to: Sender Account No. in Section 1 will be billed. Recipient Third Party Credit Card Cash/Check

Total Packages _____ Total Weight _____ Total Charges _____
Credit Card Auth. _____
* Our liability is limited to \$100 unless you declare a higher value. See the FedEx Service Guide for details.

8 Release Signature *Sign to authorize delivery without obtaining signature.*

By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.
Questions? Call 1-800-Go-FedEx (800-463-3339)
Visit our Web site at www.fedex.com

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