

ANADA 200-244
HFA 305

OCT 22 1999

ANADA Approval Date: _____

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200 - 244

TUCOPRIM[®] Powder

TUCOPRIM[®] (sulfadiazine and trimethoprim) is indicated for the control of bacterial infections of horses during treatment of acute strangles, respiratory tract infections, acute urogenital infections, wound infections, and abscesses.

Sponsored by:

Pharmacia & Upjohn Co.
7000 Portage Road
Kalamazoo, Michigan 49001

FOIS 1

FREEDOM OF INFORMATION SUMMARY

1. General Information

ANADA: 200-244

Sponsor: Pharmacia & Upjohn Co.
7000 Portage Road
Kalamazoo, Michigan 4900 1

Trade Name: TUCOPRIM® Powder

Generic Name: trimethoprim/sulfadiazine powder

Dosage Form: TUCOPRIM Powder is a formulation of 333 mg sulfadiazine and 67 mg trimethoprim per gram in a calcium carbonate (limestone) base.

How Dispensed: Rx 3

Route of Administration: Orally in the feed

Species: Equine

Indications for Use: For control of bacterial infections of horses during treatment of acute strangles, respiratory tract infections, acute urogenital infections, wound infections, and abscesses.

Labeled Dosage: The recommended dosage is 3.75 g TUCOPRIM Powder per 110 lbs (50 kg) body weight. This provides 250 mg of trimethoprim and 1250 mg of sulfadiazine per 110 lbs body weight.

The product should be administered once daily in a small amount of palatable feed for five to seven days or for two or three days after clinical symptoms have subsided.

Pioneer Product: UNIPRIM Powder, manufactured by Macleod Pharmaceuticals, Inc. (ANADA 200-033)

2. Target Animal Safety and Drug Effectiveness

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA, 53 FR 50460, 15 December 1988, First GADPTRA Policy Letter), an abbreviated new animal drug application (ANADA) may be submitted for a generic version of an approved new animal drug. New target animal safety, drug effectiveness data, and human food safety data are not required. The sponsor relies on the efficacy and target animal safety of the pioneer product, based on established bioequivalence between the two formulations. In this case, a waiver from the requirement to conduct an *in vivo* bioequivalence study (fifth GADPTRA Policy Letter: Bioequivalence Guideline, 12 April 1990) was granted based on the chemical similarity of the products. The generic product contains the same active and inactive ingredients, all in the same concentration as the pioneer product. The generic product is also the same dosage form, an oral powder, as the pioneer product.

3. Human Safety

This product has the following WARNING statements on the label, "Not for human use. Keep out of reach of children. Not for use in horses intended for food".

Human food safety data are not required.

4. Agency Conclusions

This ANADA submitted under section 512(b) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the Act and demonstrates that when Tucoprim[®] Powder (sulfadiazine and trimethoprim oral powder) is used under the proposed conditions of use, it is safe and effective for its labeled indications.

Attachments:

generic product labeling
pioneer product labeling

NDC0009-7703-01 200 grams

TUCOPRIM®

Powder

**trimethoprim and
sulfadiazine**

67 mg trimethoprim and
333 mg sulfadiazine per gram

For use in Horses

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

ANADA #200-244,
Approved by FDA

Indications: TUCOPRIM Powder is indicated in horses
where potent systemic antibacterial action against
sensitive organisms is required. TUCOPRIM Powder
is indicated where control of bacterial infections is
required during treatment of acute strangles, acute
urogenital infections, respiratory tract infections,
wound infections and abscesses.

TUCOPRIM Powder is well tolerated in foals.

Dosage: The recommended dose is 3.75 g TUCOPRIM
Powder per 110 lb. (50 kg) body weight per day.
Each level scoop contains 17.0 grams which is
sufficient to treat 500 lbs of body weight. 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.

See package insert for complete product information.
Warning: Not for human use. Not for use in horses
intended for food.

Store at or below 30°C.

802 033 000

Coda 50171/1

Manufactured in The United Kingdom
For: Pharmacia & Upjohn Company
Kalamazoo, Michigan 49001, USA

By: Pharmacia & Upjohn Animal Health Limited
Corby, Northants NN17 4DS, England

LOT:
EXP:

Pharmacia
& Upjohn

Pharmacia & Upjohn

Composition Unit 2566

PRODUCT

NDC0009-7703-02 2000 grams

TUCOPRIM[®]
Powder

**trimethoprim and
sulfadiazine**

67 mg trimethoprim and
333 mg sulfadiazine per gram

For use in Horses

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

ANADA #200-244,
Approved by FDA

LOT:
EXP:

Indications: TUCOPRIM Powder is indicated in horses
where potent systemic antibacterial action against
sensitive organisms is required. TUCOPRIM Powder
is indicated where control of bacterial infections is
required during treatment of acute strangles, acute
urogenital infections, respiratory tract infections,
wound infections and abscesses.

TUCOPRIM Powder is well tolerated in foals.

Dosage: The recommended dose is 3.75 g TUCOPRIM
Powder per 110 lb. (50 kg) body weight per day.
Each level scoop contains 17.0 grams which is
sufficient to treat 500 lbs of body weight. 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.

See package insert for complete product information.
Warning: Not for human use. Not for use in horses
intended for food.

Store at or below 30%.

802 032 000

Code 50171/2

Manufactured in The United Kingdom
For: Pharmacia & Upjohn Company
Kalamazoo, Michigan 49001, USA

By: Pharmacia & Upjohn Animal Health Limited
Corby, Northants NN17 4DS, England

Packet Label (1125 g Size)



MACLEOD
PHARMACEUTICALS INC
NOC 58711-3010-2

UNIPRIM™

POWDER FOR HORSES

Each gram contains: 67mg Trimethoprim, 333mg Sulfadiazine

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

Recommended Dose: 3.75g per 110 lbs (50kg) body weight once daily in a small amount of palatable feed. A level scoop contains 37.5g, sufficient to treat 1100 lb (500kg) body weight.

See package insert for additional information.

Store at or below 30°C (86°F)

ANADA # 200-033, approved by FDA

Warning: Not for use in horses intended for food.

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

KEEP OUT OF REACH OF CHILDREN

Manufactured for
Macleod Pharmaceuticals, Inc.
Fort Collins, CO 80525 USA

Net Contents 1125 grams

UP093755 Rev: 4/96

Label for the Shipper Bucket (1125 g Size)

MACLEOD
PHARMACEUTICALS, INC.

UNIPRIM

POWDER FOR HORSES

STORE AT OR BELOW 30°C (86°F)

6 PACKETS X 1125 GRAMS

EXP. DATE

LOT No.

UP093757 Rev. 4/96

Packet Label (37.5 g Size)

200-033

7-10-97



MACLEOD
PHARMACEUTICALS INC

NDC 58711-3010-1

UNIPRIM™

POWDER FOR HORSES

Each gram contains: 67mg Trimethoprim, 333mg Sulfadiazine

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

Recommended Dose: 3.75g per 110lbs (50kg) body weight once daily in a small amount of palatable feed.

See package insert for additional information.

Store at or below 30°C (86°F)

ANADA # 200-033, approved by FDA

Warning: Not for use in horses intended for food.

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

KEEP OUT OF REACH OF CHILDREN

Manufactured for
Macleod Pharmaceuticals, Inc.
Fort Collins, CO 80525 USA

Net Contents 37.5 grams

UP093751 Rev. 4/96

Box Label (37.5 g Size)



MACLEOD
PHARMACEUTICALS INC

NDC 58711-3010-1

UNIPRIM™

POWDER FOR HORSES

Each gram contains: 67mg Trimethoprim, 333mg Sulfadiazine

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

Recommended Dose: 3.75g per 110lbs (50kg) body weight once daily in a small amount of palatable feed.

See package insert for additional information.

Store at or below 30°C (86°F)

ANADA # 200-033, approved by FDA

Warning: Not for use in horses intended for food.

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

KEEP OUT OF REACH OF CHILDREN

Manufactured for
Macleod Pharmaceuticals, Inc.
Fort Collins, CO 80525 USA

UP093753 Rev. 4/96

30 PACKETS x 37.5 GRAMS

Exp. Date
Lot No.

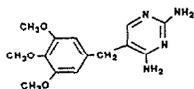
TUCOPRIM® Powder

For Use in Horses

Pharmacia
&Upjohn

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 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/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>Bacillus</i>	<i>Pseudomonas</i>
<i>Salmonella</i>	<i>Fusiformis</i>		<i>Erysipelothrix</i>
<i>Pasturella</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 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-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

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.

Pharmacology

Following oral administration, trimethoprim/sulfadiazine is rapidly absorbed and widely distributed throughout body tissues and blood. The levels 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 trimetho-

NDC 0009-7703-02 2000 grams

TUCOPRIM® Powder

trimethoprim and
sulfadiazine

67 mg trimethoprim and
333 mg sulfadiazine per gram

For use in Horses

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

ANADA #200-244
Approved by FDA

Pharmacia & Upjohn

TUCOPRIM Powder

prim and sulfadiazine, as measured in either serum or plasma, in 24 adult horses observed after a single dose of TUCOPRIM Powder:

AVERAGE 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	<0.25	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
- Respiratory Tract Infections
- Acute Urogenital 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 45% 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 3.25 g TUCOPRIM Powder per 110 lb (50 kg) body weight per day. Each level scoop contains 17.0 grams which is sufficient to treat 500 lbs of body weight. 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 45% 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 NDC 0009-7703-01
2000 gram pails NDC 0009-7703-02

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

ANADA #200-244, Approved by FDA

Manufactured in the United Kingdom

For: Pharmacia & Upjohn Company, Kalamazoo, MI 49001, USA

By: Pharmacia & Upjohn Animal Health Limited

7 Godwin Road, Earlsfrees Industrial Estate

Corby, Northants, NN17 4DS, England

May 1999

802 610 000