Approval Date: August 5, 1996

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 100-929

B. Sponsor

Pfizer Inc.
Animal Health Group
812 Springdale Drive
Exton, PA 19341-2803

C. Proprietary Name

Primor® Tablets

D. Established Name

sulfadimethoxine/ormetoprim

E. Dosage Form

Tablet

F. Dispensing Status

Rx

G. Dosage Regimen

Administer an initial oral dose of 25 mg/lb (55 mg/kg) of body weight on the first day of treatment. Administer subsequent daily doses at the rate of 12.5 mg/lb (27.5 mg/kg) of body weight. Continue treatment for at least two days after remission of clinical signs. Do not extend treatment for more than 21 consecutive days.

Suggested dosage schedules follow:

Product	Body Weight (lbs) Up to	No. of Tablets First Day	No. of Tablets Subsequent Days
Primor 120	5	1	1/2
Primor 120	10	2	1
Primor 120	15	3	1 1/2
Primor 240	10	1	½
Primor 240	20	2	1
Primor 240	30	3	1 1/2
Primor 600	25	1	½
Primor 600	50	2	1
Primor 1200	50	1	½
Primor 1200	100	2	1

H. Route of Administration

Oral

I. Indication

Primor is for the treatment of skin and soft tissue infections (wounds and abscesses) in dogs caused by strains of *Staphylococcus aureus* and *Escherichia coli* and urinary tract infections caused by *Escherichia coli*, *Staphylococcus* spp., and *Proteus mirabilis* susceptible to sulfadimethoxine/ormetoprim.

J. Effect of Supplement

This supplemental Application amends the NADA to provide for the use of Primor; Tablets for the treatment of urinary tract infections caused by certaom bacteroa susceptible to sulfadimethoxine/ormetoprim. Primor® Tablets (NADA 100-929) is currently approved for use in dogs.

II. EFFECTIVENESS

A clinical field study was initiated to determine the safety and efficacy of Primor (sulfadimethoxine and ormetoprim in 5:1 ratio) for the treatment of canine urinary tract infections.

The treatments were evaluated for efficacy by the veterinary investigator using a clinical scale based on:

1. resolution of clinical signs;
2. resolution of the bacterial infections based on pre-treatment and post-treatment urinalysis and sterile urine culture; and

3. the necessity for additional therapy.

Physical examination, hematology, blood chemistry and presence or absence of adverse reactions were the parameters to determine safety.

The well-controlled, blinded trial was conducted at study sites over three geographic regions. An identical protocol common to all sites was used to compare Primor to a positive control, Tribrissen (sulfadiazine and trimethoprim). Blinding was accomplished through the use of a separate, dispensing investigator and by packaging of investigational supplies. Animals entering the study were assigned to treatment groups on a random basis according to a randomization table provided to the investigator with the study protocol.

Dogs of any breed and weight and either sex with acute, naturally occurring urinary tract infections of bacterial origin were admitted to the study. The diagnosis of the urinary tract infection was based on the animal showing clinical signs of a urinary tract infection (e.g. increased frequency of urination, decreased volume of urine voided, hematuria, stranguria and urgency) and laboratory confirmation of the infection by urinalysis, and bacterial culture and sensitivity.

Animals were excluded from the study due to:

1. known or suspected allergic potential to either the experimental or control drug;
2. treatment for the same condition within three weeks prior to entering the study;
3. pregnancy or the animals being used for breeding purposes;
4. co-existing disease impacting the urinary system (i.e. cancer, uroliths, persistent urachus, diabetes mellitus, Cushing's Disease);
5.
6. concurrent use of topical or systemic anti-bacterial drugs, antibiotics or antibacterial agents; and
7. chronicity of the condition requiring repeated or prolonged treatment.

Permissible diagnostic and therapeutic procedures included: radiography, pneumocystography, double contrast cystography and related sedation or anesthesia, as well as flushing of the urinary bladder with normal saline or electrolyte solution. However, the urinary bladder could not be flushed with antiseptic or antibacterial solutions (i.e. chlorhexidine or betadine).

All dogs were treated orally. Both drugs were dosed per label instructions: Primor at 25 mg/lb body weight once daily on the first day of treatment followed by 12.5 mg/lb body weight once daily on subsequent days of treatment; and Tribrissen at 12 mg/lb once daily throughout the course of treatment. The duration of therapy was for a minimum of ten days and a maximum of fourteen days.

A pre-treatment evaluation was conducted on day 0. That included:

1. physical examination (with measurement of temperature);
2. documentation of clinical signs;
3. blood hematology and chemistry; and
4. urinalysis, urine culture and sensitivity. Urine samples were always collected by cystocentesis.

An interim documentation of clinical signs and temperature measurement was repeated on day 3 and day 7. The post-treatment evaluation of day 13 or 17 included:

1. temperature measurement;

2. documentation of clinical signs;
3. blood hematology and chemistry; and
4. urinalysis and urine culture.

Clinical efficacy was evaluated by the investigator and classified into one of the following categories:

1. excellent;
2. good;
3. fair; or
4. poor (failure).

All dogs entered into the study and administered the experimental or control drug were evaluated for safety. All investigators were instructed to report any adverse reactions to the sponsor. A total of 7 adverse reactions were reported, 3 with Primor and 4 with Tribrissen. There were also 10 cases with a total of 16 notable changes in hematology and clinical chemistry parameters, 7 with Primor and 9 with Tribrissen.

Overall Results

This study was conducted as a multicentered trial involving nine investigators. There were 75 dogs with urinary tract infections that were treated with either experimental or control drug and completed the study protocol.

Clinical Investigators and Addresses:

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Bacteriological Results

The 75 dogs with urinary tract infections that completed the study protocol had a total of 76 bacterial isolates from the pre-treatment culture. One dog was found to be infected with both *E. coli* and *Proteus mirabilis*. The number of cases infected with any particular isolate are summarized in the following table.

Of the 76 bacterial isolates, 43 were treated with Primor and 33 were treated with Tribrissen. Those treated with Primor had an overall elimination rate of 93% versus an overall elimination rate of 90% for Tribrissen treated isolates. For *E. coli*, the most common isolate, the elimination rate with Primor was 87% and with Tribrissen it was 86%. The next most common isolate, *Proteus mirabilis*, had elimination rates of 92% and 100% for Primor and Tribrissen, respectively. For *Staphylococcus* spp., the elimination rates were 100% and 83% for Primor and Tribrissen respectively. The elimination rates for each of the isolates are outlined in the following table.

(Eds note: The following table consists of 7 columns).
Bacteriological Response to Treatment By Therapy and Organism Treated

Pre-Treatment Bacterial Isolate	PRIMOR-Total No.	PRIMOR- No. Elim.	PRIMOR- % Elim.	TRIBRISSEN-Total No.	TRIBRISSEN-No. Elim.	TRIBRISSEN-% Elim
E. coli	23	20	87%	22	19	86%
Proteus Mirabillis	12	11	92%	5	5	100%
Staphylococcus spp., (see note*)	8	8	100%	6	5	83%
TOTAL	43	39	91%	33	29	88%

Note * = Includes *S. aureus* and *S. intermedius*.

Clinical Response Results

At the end of therapy, the clinical investigator graded the clinical response to treatment as excellent, good, fair or poor. Excellent and good ratings, which required no further antibiotic therapy, were considered a positive response to therapy. Fair and poor ratings, which required additional antibiotic therapy, were considered a negative response to therapy.

Of the 75 cases that completed the study protocol, 42 were treated with Primor and 33 were treated with Tribrissen. One dog had both *E. coli* and *Proteus mirabilis*. The following table contains a summary of the clinical response to therapy by treatment, bacterial isolate and grade.

E. coli

Clinical Response to Therapy By Treatment

	PRIMOR		**TRIBRISSEN**	
Clinical Efficacy Grade	**No. of Cases**	**Response to Therapy**	**No. Cases**	**Response to Therapy**
Excellent	15	65%	16	72%
Good	3	13%	2	9%
Fair	4	18%	1	5%
Poor	1	4%	3	14%
Totals	23	100%	22	100%

Proteus mirabilis

Clinical Response to Therapy By Treatment

	PRIMOR		**TRIBRISSEN**	
Clinical Efficacy Grade	**No. of Cases**	**Response to Therapy**	**No. Cases**	**Response to Therapy**
Excellent	8	67%	4	80%
Good	1	8%	1	20%
Fair	2	17%	0	0%
Poor	1	8%	0	0%
Totals	12	100%	5	100%

***Staph*. spp.**

Clinical Response to Therapy By Treatment

	PRIMOR		**TRIBRISSEN**	
Clinical Efficacy Grade	**No. of Cases**	**Response to Therapy**	**No. Cases**	**Response to Therapy**
Excellent	8	100%	5	83%
Good	0	0%	1	17%
Fair	0	0%	0	0%
Poor	0	0%	0	0%
Totals	8	100%	6	100%

Clinical evaluation: Four categories; Excellent and Good were considered "positive responses" and Fair and Poor were considered "negative responses".

Excellent
1. clinical signs resolved
2. urine culture negative for original pathogen
3. additional antibiotic therapy not necessary

Good
1. clinical signs resolved
2. urine culture negative for original pathogen
3. one or more of urinalysis parameters abnormal
4. additional antibiotic therapy not necessary

Fair:
a. diminished clinical signs
b. urine culture positive for orginial pathogen, but CFU are much less
c. one or more of urinalysis parameters abnormal
d. additional antibiotic therapy needed

Poor:
a. clinical signs same or worse
b. urnine culture positive for original pathogen and CFU are = or > than original
c. urinalysis parameters are same or worse
d. change of antibiotics is indicated

Study Conclusions
Based on the bacteriologic cure rates (comparison of pre- and post-treatment bacterial culture), clinical cure rates, and low incidence of reported adverse reactions, it can be concluded that Primor is safe and efficacious for the treatment of canine urinary tract infections caused by *Escherichia coli, Staphylococcus* spp. (see Note *), and *Proteus mirabilis*.
*Note = includes *S. aureus* and *S. intermedius*. End Note.

III. ANIMAL SAFETY

Cross reference the existing FOI Summary for Primor Tablets (NADA 100-929).

The original FOI summary contains a description of the safety study that was conducted to support the approval of this product. The safety data include both laboratory and clinical evaluations conducted in accordance with existing FDA guidelines. Primor tablets will be used in the same species at the same dosage as labeled in the original approval.

IV. HUMAN SAFETY

A. Human Safety Relative to Food Consumption

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. This product is labeled as a prescription drug for use only in dogs, which are non-food animals.

B. Human Safety Considerations Other Than Food Safety

In regard to possession, handling, and administration, labeling contains the statements: "NOT FOR USE IN HUMANS - For Use In Dogs Only" and "KEEP OUT OF REACH OF CHILDREN."

V. AGENCY CONCLUSIONS

The data in support of this supplemental NADA satisfy the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. The data demonstrate that Primor (sulfadimethoxine/ormetoprim), when used under the labeled conditions of use, is safe and effective.

According to the Center's supplemental approval policy (21 CFR 514.106), this is a Category II change. This supplement provides for the additional claim to include the treatment of urinary tract infections in dogs. The approval of this change has no adverse effect on the safety and effectiveness of the new animal drug. Accordingly, this approval

did not require a reevaluation of the safety and effectiveness data in the parent application.

For this supplement, the drug is restricted to use by or on the order of a licensed veterinarian because professional expertise and proper diagnosis are required to determine when a urinary tract infection is present and when treatment is necessary.

Section 512(c)(2)(F)(iii) of the Generic Animal Drug and Patent Term Restoration Act of 1988, provides for a three year period of exclusivity for a supplemental application which contains reports of new clinical or field investigations (other than bioequivalence studies) essential to the approval of the supplement and conducted or sponsored by the applicant. This supplemental NADA qualifies for such an exclusivity period (new claim only), which will expire three years from the date of approval.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.