Approval Date: November 24, 1989

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 100-929

B. Sponsor

Hoffmann-La Roche Inc.
340 Kingsland St.
Nutley, NJ 07110

C. Proprietary Name

Primor Tablets

D. Established Name

sulfadimethoxine/ormetoprim

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Tablets

G. Dispensing Status

Rx

H. 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:

Suggested Primor Dose Schedule

	Body Weight (lbs.) Up to	**No. of Tablets First Day**	**No. of Tablets Subsequent Days**
Primor 120	5	1	1/2
	10	2	1
	15	3	1 1/2
Primor 240	10	1	1/2

	Body Weight (lbs.) Up to	**No. of Tablets First Day**	**No. of Tablets Subsequent Days**
	20	2	1
	30	3	1 1/2
Primor 600	25	1	1/2
	50	2	1
Primor 1200	50	1	1/2
	100	2	1

I. Route of Administration

Oral

J. Indication

Primor is to be used in the treatment of skin and soft tissue infections (wounds and abscesses) in dogs caused by strains of *Staphylococcus aureus* and *Escherichia coli* susceptible to sulfadimethoxine/ormetoprim.

II. EFFECTIVENESS

Primor is an antimicrobial drug containing sulfadimethoxine and ormetoprim in a five to one ratio. Ormetoprim is used as a potentiator to enhance the antibacterial effect of the active ingredient.

A potentiator of a systemic antimicrobial agent is a substance used to augment the antibacterial spectrum of the active ingredient by protecting it from bacterial enzyme inactivation or by affecting the metabolic pathways of microorganisms at different points than the active ingredient. A potentiator is not an active ingredient per se that would be used alone therapeutically. Therefore, Primor is not a combination drug.

The effectiveness of Primor was established by the following pivotal studies.

A. Pivotal Studies

1. *In vitro* Laboratory Studies:

a. Determination of Optimum Ratio of Sulfadimethoxine (SDM) to Ormetoprim (OMP).

Dr. G. Maestrone, Hoffmann-La Roche, determined the antibacterial activity of various ratios of SDM and OMP against three gram negative and three gram positive canine origin bacterial isolates in Mueller Hinton broth. The optimum ratio of SDM plus OMP was selected by determining the antibacterial activity of the two compounds singly as well as at ratios ranging from 1 part of SDM to 1280 parts of OMP and vice versa. The maximum synergistic effect was obtained at the 5:1 ratio of SDM to OMP.

The organisms tested were:

Streptococcus zooepidemicus (ASR No 82)

Streptococcus beta-hemolyticus (ASR No 78)

Staphylococcus aureus (ASR No 141)

Escherichia coli (ASR No 89)

Klebsiella pneumoniae (ASR No 801)

Proteus vulgaris (ASR No 803)

The fractional inhibitory concentration (FIC) of the six strains was averaged and is reported in Table 1.

The lowest FIC value (optimum ratio) 0.0778 was obtained when SDM and OMP were present at the 40:1 ratio, followed very closely by values of 0.0871 for the 5:1 ratio, and of 0.0910 for the 10:1 ratio, indicating very low FIC values for a wide range of SDM:OMP ratios.

Pharmacokinetic considerations favored the 5:1 ratio of sulfadimethoxine and ormetoprim.

Table 1 Average FIC Index of Three Gram Positive and Three Gram Negative Canine Origin Organisms

OMP RATIO	SDM	Average FIC
1	1	.1889
1	2.5	.1634
1	5	.0871
1	10	.0910
1	20	.1154
1	40	.0778
1	80	.1096
1	160	.1537
1	320	.1760
1	640	.2476
1	1280	.2655
2.5	1	.3731
5	1	.4369

OMP RATIO	**SDM**	**Average FIC**
10	1	.4764
20	1	.8856
40	1	.9228
80	1	1.8611
160	1	1.8239
320	1	1.9537
640	1	3.3302
1280	1	11.3189

b. Comparative Evaluation of the Susceptibility of 754 Canine Origin Bacterial Strains to 5:1, 20:1 and 80:1 SDM + OMP Ratios

A comparative evaluation of the susceptibility of 754 bacterial strains of canine origin to SDM and OMP at ratios of 5:1, 20:1 and 80:1 indicates no difference in the activity of the three ratios evaluated; except for the difference between the activity of the 5:1 and the 80:1 ratio against gram negative strains. This study was performed by Dr. G. Maestrone, Hoffmann-La Roche Inc.

Twenty-five mcg potency discs were used in this study which included 344 gram positive strains representing six genera and 410 gram negative strains representing seven genera. Incidence of resistance of the gram positive strains to SDM was 28%, that of the gram negative strains was 47%, with an overall incidence of 39% resistance to SDM.

Among the gram positive strains there was an overall 8, 9 and 11% incidence of resistance to the 5:1, 20:1 and 80:1 SDM + OMP ratio, respectively. Only 27, 31 and 36% of the 98 SDM resistant strains were resistant to the SDM + OMP 5:1, 20:1 and 80:1 ratios.

Among the gram negative strains there was an overall 27, 29 and 34% incidence of resistance to the 5:1, 20:1 and 80:1 SDM + OMP ratios, respectively. Only 56, 61 and 70% of the 194 SDM resistant strains were resistant to the SDM + OMP 5:1, 20:1 and 80:1 ratios. Resistance percentages included 47 pseudomonas and 3 alcaligenes strains known to be resistant to the SDM + OMP potentiated sulfonamide.

An overall 18, 20 and 24% incidence of resistance to the 5:1, 20:1 and 80:1 SDM + OMP ratios was observed for the 754 strains, against a 39% incidence of resistance to SDM.

Evaluation of the data obtained in this study indicate that the percentages of gram positive and gram negative bacterial strains resistant to the SDM + OMP

5:1, 20:1 and 80:1 ratios were considerably lower than the corresponding SDM percentages.

Table 2 Percent Resistance to Sulfadimethoxine (SDM) and Various Ratios of Sulfadimethoxine and Ormetoprim (OMP).

Treatment	Percent Strains Resistant - 344 Gram Positive	Percent Strains Resistant - 410 Gram Negative
SDM, 250 mcg disc	28.5	47.3
SDM + OMP 5:1, 25 mcg disc	7.6	26.6
SDM + OMP 20:1,25 mcg disc	8.7	29.3
SDM + OMP 80:1,25 mcg disc	11.0	33.9

2. In Vivo Study (Dogs)

The purpose of this study was to evaluate the therapeutic efficacy of Primor (sulfadimethoxine + ormetoprim 5:1) in an experimentally induced soft tissue infection in dogs and to compare it to that of sulfadimethoxine and of ormetoprim used singly.

Twenty purebred beagles (equal number of male and female), ranging in age from 11 to 18 months and in weight from 7.2 to 13.4 kg, were infected subcutaneously at four ventral sites with a strain of *Escherichia coli* resistant to penicillin, erythromycin, streptomycin, and sulfonamides. Treatment groups consisted of: 1) Primor at 55 mg/kg (25 mg/lb) b.w. on day one, followed by 7 consecutive daily doses of 27.5 mg/kg (12.5 mg/lb) (4M & 4F); 2) sulfadimethoxine at 55 mg/kg (25 mg/lb) on day one, followed by 7 consecutive daily doses of 27.5 mg/kg (12.5 mg/lb) (4M & 4F); 3) ormetoprim at 9.2 mg/kg (4.2 mg/lb) on day one, followed by 7 consecutive daily doses of 4.6 mg/kg (2.1 mg/lb) (2M & 2F); and 4) placebo (2M & 2F). The drugs were administered orally, as suspensions.

Clinical and microbiological criteria employed to evaluate the efficacy of the treatments included body temperature, daily lesion scores (size and severity of the lesions), and microbiological re-isolation of the causative organisms. Following is a summary table of the four treatment regimens. (Table 3).

Table 3 Therapeutic Efficacy of SDM + OMP (Primor), SDM and OMP Against Experimentally Induced Escherichia coli Soft Tissue Infection in Dogs

Treatment Group	Parameter	Days Post Infection - 1	Days Post Infection - 2	Days Post Infection - 3	Days Post Infection - 4	Days Post Infection - 5	Days Post Infection - 6	Days Post Infection - 7	Days Post Infection - 8	Days Post Infection - 15
Sulfadimethoxine + Ormetoprim 5:1 **(24 lesions)**	Lesion size(1)	4	4	15	19	24	39	51	59	92
	Clinical score (1)	38	41	31	24	49	53	55	74	97
	Micro. (2)	100	100	71	63	58	58	58	58	58
Sulfadimethoxine **(24 lesons)**	Lesion size	-66	-41	-33	-11	-16	-15	16	28	86
	Clinical score	-25	-53	-59	-50	-53	-40	-27	24	94
	Micro.	100	100	71	50	38	38	33	33	33
Ormetoprim **(16 lesions)**	Lesion size	-39	-19	-5	-4	12	11	23	28	81
	Clinical score	-12	-40	-52	-45	-43	-36	-14	24	88
	Micro.	100	100	75	38	38	38	38	38	38
Placebo **(16 lesions)**	Lesion size	-65	-18	-13	-5	5	18	33	37	85
	Clinical score	-6	-40	-45	-62	-48	-48	-16	22	92
	Micro.	100	81	69	38	31	25	25	25	25

(1) Reported as % improvement over observations made prior to starting treatment
(2) Reported as % of negative over a possible 100% positive

The distinct effect/no effect results obtained in this study show, without the need for statistical analysis, that Primor, sulfadimethoxine and ormetoprim in a ratio of 5:1, is the therapeutically more effective than either sulfadimethoxine or ormetoprim administered singly (Dr. G. Maestrone, Hoffmann-La Roche Inc).

3. Dose Titration

a. Clinical

The efficacy of three dose levels of Primor, 5:1 ratio of sulfadimethoxine and ormetoprim, was compared with a negative placebo and an approved, positive control drug (Di Trim) in an acute urinary tract infection model in dogs produced with *Escherichia coli*. Dosing regimens of one half, one and two times the recommended use level were compared to non-medicated controls and positive control medicated with a commercially available potentiated

sulfonamide. The dosing schedule and results are shown in Table 4. The specific clinical and laboratory criteria used in the model clearly define the diagnostic and therapeutic end points (G.V. Ling, et al., Am. J. Vet. Res. 40, 1605-1612 (1979) and 41, 686-690 (1980). This was a blinded study. Treatments were allocated and administered by a person not responsible for clinical observations and with no knowledge of laboratory results.

Dogs were treated for ten consecutive days following confirmation of urinary tract infection. Laboratory data, including a complete blood count, SMA12 chemistry panel, urinalysis, and urine culture, were obtained on each dog at the end of a conditioning period, 48 hours or more after inoculation (prior to first treatment), on the fifth and tenth days of treatment, and seven days after the end of treatment. The primary laboratory criterion for the evaluation of therapeutic efficacy of the treatment drug doses was bacterial culture counts from urine specimens collected by antepubic cystocentesis. The presence of any bacteria in the urine was considered indicative of an active infection.

The comparative efficacy of the treatments given was based on the number of bacteriologic cures, the number of bacteriologic failures, and the number of bacteriologic relapses in each treatment group in comparison to untreated controls and the other treatment groups.

Variations in blood counts and blood chemistries were observed in some dogs; however, most dogs remained within normal limits throughout the experiment. Animals were monitored daily for clinical manifestations of infection and for possible side effects. No side effects related to treatment were observed.

Table 4 Efficacy of Primor Against an Experimental Acute Urinary Tract Infection in Dogs

Drug (1)	**Dose(mg/lb BW) - Day 1**	**Dose(mg/lb BW) - Day 2-10**	**Label Use**	**No. dogs per trmt**	**No. dogs cleared bacterial pathogens (2)**
Placebo	0	0	--	7	0
Primor	12.5	6.3	½	7	5
Primor	25.0	12.5	1	6	5
Primor	50.0	25.0	2	6	4
DiTrim(3)	13.6	13.6	1	6	4

(1) Administered as tablets
(2) Sterile urine at treatment day 10 and at post treatment day 7
(3) FDA approved product of Syntex-contains sulfadiazine and trimethoprim

Although effect/no effect results do not lend themselves to statistical analysis, the results of this study show that all treatments are similar, and that they are superior to placebo. (Dr. G.V. Ling, College of Veterinary Medicine, University of California).

b. Therapeutic Blood Levels:

In vitro studies have demonstrated that the ratio of ormetoprim : sulfadimethoxine must not exceed 1:1200. *In vivo* blood studies have demonstrated that at one half the recommended use level, Primor does not consistently maintain therapeutic blood levels in dogs over a 24 hour period as does the recommended use level. Sulfadimethoxine / ormetoprim blood levels achieved with an initial (loading) dose of 25 mg/lb (55 mg/kg) on day one and maintained by 12.5 mg/lb (27.5 mg/kg) body weight on day two were studied in two male and two female dogs. These were compared to levels attained in eight dogs administered one half the recommended dosing regimen (i.e., given 12.5 mg/lb day one, 6.25 mg/lb 24 hours later). A series of blood samples were taken at various times after dosing, six of which are reported in Table 5. The initial dose was administered at zero hours. The maintenance dose was administered immediately after the 24 hour sampling. The data show that at one half the recommended dose level, ormetoprim (essential for Primor's potentiated property) is not detectable 24 hours after administration, thereby precluding a one a day medication schedule. The data do demonstrate that therapeutically effective blood levels of both sulfadimethoxine/ormetoprim are obtained and maintained over a 24 hour period with the recommended Primor dosing regimen.

Table 5 Blood Levels (mcg/mL) Obtained with Recommended and One-half Recommended Primor Dosing Regimen (25or 12.5 mg/lb Followed by 12.5 or 6.25 mg/lb at 24 hours).

Sample	2 HR		8 HR		24HR*		28 HR		48 HR	
	Rec	½Rec	Rec	½ Rec	Rec	½ Rec	Rec	½ Rec	Rec	½ Rec
SDM	23	16	41	22	39	12	85	28	36	14
OMP	1.04	0.94	0.55	0.52	0.09	ND+	0.96	0.45	0.03	ND

* Sample collected before administration of the second dose.
\+ Not Detected

Since sulfonamides are bacteriostatic rather than bactericidal, adequate blood levels must be maintained for a sufficient period of time to effect a cure. Therefore, based on the clinical and blood level data, it is concluded that the recommended once a day dosing regimen for Primor is effective (orally 12.5 mg/lb (27.5 mg/kg) body weight, with a double dose on day one). (Drs. J. Fellig and G. Maestrone, Hoffmann-La Roche Inc.).

4. Blinded Clinical Dog Study:

The therapeutic efficacy of Primor tablets administered orally in the treatment of skin and soft tissue bacterial infections in dogs was evaluated in a double blind study conducted in three major geographical areas of the U.S. using the 5:1 ratio of sulfadiazine and trimethoprim as the positive control. Bacterial cultures were

taken prior to and following treatment and antibacterial sensitivities were determined. Qualifying *S. aureus* and *E. coli* cases are presented in Table 6. Twenty-six cases were treated with Primor and 25 with the control drug. The majority of the responding cases involved various infected skin wounds and abscesses. The cooperating veterinarians are listed in Table 7.

Primor tablets were administered at the recommended dose of 55 mg/kg b.w. (25 mg/lb) on day one, and at 27.5 mg/kg (12.5 mg/lb) per day for the remainder of the treatment period; the control drug was administered at the recommended dose level of 14 mg/lb/day throughout the treatment period. Duration of treatment ranged from 5 to 11 days for both drugs.

Although studies of this design are not amenable to statistical analysis, the results obtained, reported in the following table, that Primor is effective in the treatment of bacterial skin and soft tissue infections in dogs and is at least as effective as the positive control.

Table 6 Therapeutic Efficacy of Primor in Dogs-Skin and Soft Tissue Infections

Bacterial Primor ------sulfadiazine+trimethoprim 5:1------ Agent No.Treat. % Improved* No. Treated % Improved* S. aureus 16 94 13 77 E. coli 10 100 12 92 Total 26 96 25 84

*Clinical Evaluation: Excellent + Good

Name and Address of Veterinary Cooperating in the Therapeutic Evaluation of Primor Tablets in the Treatment of Soft Tissue Infections in Dogs (Double Blind Studies)

Dr. W. Anderson
Bev Labs Veterinary Hospital
2969 West 127 Street
Bleu Island, IL 60406

Dr. A. Becker
Becker Animal Hospital
322 Frontage Rd
Northfield, IL 60083

Dr. A. Black
Animal Medical Center
510 East 62nd Street
New York, NY 10021

Dr. R. Bradley
Animal Medical Center
510 East 62nd Street
New York, NY 10021

Dr. M. Frost
Herschel Animal Clinic
4030 Herschel Street
Jacksonville, FL 32205

Dr. S. Gloth
Freehold Veterinary Hospital, P.A.
Route 9
Freehold, NJ 07728

Dr. R. Imhoff
Nutley Animal Hospital
274 Washington Ave.
Nutley, NJ 07110

Dr. C. Lawson
Animal Medical Center
540 East 62nd Street
New York, NY 10021

Dr. C. Manziano
Animal Clinicla and Hospital of Jersey City
603 West Side Ave.
Jersey City, NJ 07304

Dr. D. Zawie
Animal Medical Center
510 East 62nd Street
New York, NY 10021

B. Corroborative Studies

1. *In vivo* Mouse Studies:

The potentiation effect of ormetoprim on sulfadimethoxine was demonstrated in mice with experimentally produced systemic infections caused by *Diplococcus pneumoniae, Streptococcus pyogenes, Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Salmonella schottmuelleri, Salmonella typhosa,* and *Pseudomonas aeruginosa*. The mice (6-8 per organism) were treated orally with graded doses of sulfadimethoxine, with and without concomitant administration of ormetoprim at a level (50 mg/kg b.w.) which had been shown to be inactive by itself. Six treatments, in one ml doses, were administered orally to each mouse on the following schedule: two treatments, five hours apart, on the day of and day following infection; one treatment on the second and third days following infection; with first treatment immediately after infection. The health status of each animal was reported for three days following infection and dead animals reported for 14 days following infection.

A 50% curative dose (CD 50) was calculated on the basis of the survival of the treated animals. Potentiation was considered to have occurred if the CD50 value for the sulfadimethoxine alone was consistently at least twice the CD50 value obtained with the sulfadimethoxine/ormetoprim. Potentiation of sulfadimethoxine, indicated by a decrease in the CD50 values in the presence of ormetoprim, was observed to be two to five fold with all organisms except *Pseudomonas aeruginosa*. (Dr. R. Cleeland, Hoffmann-La Roche Inc.).

2. Susceptibility to Primor of 671 Bacterial Strains of Canine Origin

A total of 671 bacterial isolates of canine origin were evaluated, by the agar diffusion method, for susceptibility to Primor (Table 8) (Dr. G. Maestrone, Hoffmann-La Roche Inc.).

Table 8 Incidence of Resistance to Primor of 671 Bacterial Strains

Organism	No. Strains	% Resistance
Gram Positive:		
Streptococcus	55	13
Hemolytic *staphylococcus*	179	6
Non-hemolytic *staphylococcus*	94	3
Diplococcus	84	21
Corynebacterium	6	--
Subtotal	418	10
Gram Negative:		
Proteus	76	28

Escherichia	74	5
Pseudomonas	87	91
Brucella	4	0
Alcaligenes	3	100
Klebsiella	9	--
Subtotal	253	42
Grand Total	671	23

3. Clinical Dog Studies

The therapeutic efficacy of Primor tablets administered at the dose level of 55 mg/kg (25 mg/lb b.w.) on day one, followed by consecutive daily doses of 27.5 mg/kg (12.5 mg/lb b.w.) was confirmed in the treatment of 217 clinical cases in dogs caused by bacterial agents.

This study was conducted at 13 veterinary facilities representing various geographical areas of the U.S. A list of these facilities is given in Table 9. Dogs of different breed, weight, sex and age were used in this evaluation and, whenever feasible, bacterial agents were isolated, identified and their susceptibility to antibacterial agents established before and after treatment. Evaluation of the treatment was based on change in clinical symptoms and in laboratory findings. Infections of the respiratory, digestive and urogenital tracts and of soft tissues were treated using Primor as the only chemotherapeutic agent with the following results:

		Response			
Infection Site	**Cases Treated**	**Cured No. Cases**	%	**Cured + Improved No. Cases**	%
Respiratory	91	74	81	82	90
Digestive	39	36	92	38	97
Urogenital	31	27	87	30	95
Soft Tissue	56	51	91	53	95
TOTAL	217	188	87	203	94

Veterinarians Cooperating in the Therapeutic Evaluation of Primor Tablets

Clinical Investigators

James G. Fish,Jr. DVM
San Juan Animal Hospital
4519 San Juan Ave.
Jacksonville, FL 31544

Wesley T. Osthus, DVM
Highway 51 South
Clinton, IL 61727

John O. McNellis, DVM
West Orange Animal Hospital
360 Northfield Ave. West Orange, NJ 07052

Dennis Stubblefield, DVM
Route 136 West
Rantoul, IL 61366

Thomas Owings, DVM
517 West Fairchild St.
Danville, IL 61832

Edward Fleischli, DVM
Pound Ridge Vet. Clinic
Scotts Corner
RR 3, Box 15A
Pound Ridge, NY 10576

Joseph Marion, DVM
Monroe Animal Hospital
Route 17M
Money, NY 10950

Robert A. Lathan, DVM
810 Main St.
Erie, IL 61250

J.L. Schoon, DVM
517 West Fairchild St.
Danville, IL 61832

Clifford E. Loomis, DVM
1100 South First Ave.
Ottawa, IL 61832

George Richards, DVM
Hillcrest Veterinary Clinic
3007 East Main
Danville, IL 61832

G. Maestrone, DVM
Animal Health Research
Hoffmann-La Roche Inc.
Nutley, NJ 07110

Wallace E. Brandt, DVM
PO Box 187
Flanagan, IL 61740>
(Now w/Hoffmann-La Roche)

III. ANIMAL SAFETY

A. Pivotal Studies

1. Acute Toxicity Dogs:

The purpose of this study was to evaluate the level at which orally administered (in gelatin capsule) sulfadimethoxine (SDM) and ormetoprim (OMP) individually, and jointly in a 5:3 ratio produced toxicity symptoms. This was accomplished by doubling (i.e., pyramiding) the initial dose of 5 mg drug activity/kg (2.3 mg/lb) body weight on successive days, excluding weekends. The individual components were each tested in single but different dogs and the SDM/OMP (5:3 ratio) was tested in two dogs, in accordance with the following schedule:

Drug (mg/kg body weight)

Dose No.	SDM - Dog Number 1	OMP - Dog Number 2	SDM/OMP - Dog Number 3 & 4	
1	5	5	3.125/1.875	=5
2	10	10	6.25/3.75	=10
3	20	20	12.5/7/5	=20
4	40	40	25/15	=40
5	80	80	50/30	=80
6	160	160	100/60	=160

Dose No.	SDM - Dog Number 1	OMP - Dog Number 2	SDM/OMP - Dog Number 3 & 4	
7	320	320	200/120	=320

The 5:3 dosing regimen provided a more severe ormetoprim challenge than will be experienced with the 5:1 ratio provided by Primor. Blood sugar and cholesterol determinations were made before initial dosing and one hour following each dose. Blood counts, hemoglobin and hematocrit were performed before treatment and after final dosing. Observations of symptoms and appetite were also made (Dr. R. Banziger, Hoffmann-La Roche Inc.).

Results of this study were as follows:

Sulfadimethoxine only: A single dog receiving pyramiding daily doses of up to 320 mg/kg (145 mg/lb) tolerated the drug without side effects. There were no significant effects of blood sugar, serum cholesterol or other blood values.

Ormetoprim only: A single dog receiving pyramiding daily doses of up to 160 mg/kg (73 mg/lb) became convulsive and drug administration was stopped. The dog survived the five day observation period. There were no significant changes in serum cholesterol or blood values. Blood sugar was elevated on the sixth dose day.
Sulfadimethoxine/Ormetoprim: The two dogs receiving pyramiding daily doses of up to 320 mg active drug/kg b.w. (145 mg/lb) survived. There were no significant changes noted in blood sugar, serum cholesterol or other blood values.

One dog (6.35 kg) showed signs of depression at doses of 160 and 320 mg/kg (73 and 145 mg/lb) of body weight and slight tremors after the 320 mg/kg dose. Throughout the observation period all food was consumed and the dog appeared normal at the end of the five day observation period post drug.

A second dog (10.45 kg) showed slight tremors at 40 to 80 mg/kg (18 to 36 mg/lb) body weight, increased motor activity and tremors at 160 mg/kg (73 mg/lb), but ate all food up to the 160 mg/kg (73 mg/lb) dose. At 320 mg/kg (145 mg/lb) there were convulsions later in the day and the dog did not eat. During the five day post drug observation period the dog ate all food presented and appeared to be normal.

The 320 mg/kg dose is approximately five times the proposed initial dose for Primor and ten times the maintenance dose. No sustaining long term effects were observed following the pyramiding doses. The conclusion is that Primor is safe to use in dogs at the proposed dosage of 55 mg/kg initially followed by a 27.5 mg/kg maintenance dose.

2. Subacute Toxicity Dogs:

An eight week oral toxicity study was conducted in forty two beagle dogs with Primor (sulfadimethoxine + ormetoprim, 5:1). The compounds were administered together in the market dosage form designed for clinical veterinary use. Dosages were 0 (control), 0 (excipient), 27.5, 82.5, or 137.5 mg/kg (12.5, 37.5, or 62.5 mg/lb)b.w./day. The drug levels used represent at least 1x, 3x and 5x the label dose level, administered for approximately three times the maximum 21 day duration provided by label direction. This length of administration was

approximately eight times the five to seven day use period anticipated in clinical situations.

The high dose and the control group contained six dogs/sex/group and the mid dose, low dose and excipient groups contained three dogs/sex/group. Following the eight week treatment period, three dogs/sex/group were necropsied and the remaining high dose and control group dogs (3/sex/group) were observed for a 12 week recovery period prior to necropsy.

Treatment of dogs with Primor at 137.5 mg/kg (62.5 mg/lb) b.w./day for eight weeks resulted in a low incidence of mild clinical signs; minimal corneal and lens opacities; reduced heart rate and R wave amplitude; decreased hemoglobin and hematocrit; decreased serum T3, T4, and folate; elevated serum cholesterol; increased thyroid, pituitary, liver and prostate weights; parenchymatous thyroid hyperplasia; enlarged basophilic cells in the pituitary; involution of the thymic cortex, slight histologic changes in the adrenal cortex; areas of vacuolization and rarefication of hepatocytes limited, focal testicular atrophy. At the end of a 12 week recovery period, the enlarged thyroids had markedly decreased in average weight but were still heavier than the control thyroids, diffuse colloidal goiter was present indicating recovery of function, and treatment related lens opacities were still present in one of two dogs that exhibited this change at the end of the treatment period. All other changes were totally reversible.

Treatment of dogs with Primor at 82.5 mg/kg (37.5 mg/lb)b.w./day for eight weeks resulted in minimal, transient corneal opacities; decreased heart rate and R wave amplitude; decreased hematocrit; decreased T3,T4 and folate values; increased serum cholesterol values; increased thyroid, pituitary, liver, and prostate weights; parenchymatous thyroid hyperplasia; enlarged basophilic cells in the pituitary and slight histologic changes in the adrenal cortex. The incidence and severity of these changes were reduced when compared to the high dose group.

Treatment of dogs with Primor at 27.5 mg.kg (12.5 mg.lb)b.w./day for eight weeks resulted in elevated serum cholesterol, increased thyroid and liver weights, enlarged basophilic cells in the pituitary and mild follicular thyroid hyperplasia.

Based on reversal of virtually all treatment related effects observed with the high dose dogs, it is concluded that the principal treatment related effects of extended or excessive Primor usage is hypothyroidism. Such effects are known effects of sulfonamides per se and are not considered unique to Primor (Dr. T.J. Hayes, Hoffmann-La Roche Inc.).

3. Chronic Toxicity Dogs:

A 13 week toxicity study was conducted in dogs which sulfadimethoxine/ormetoprim (SDM/OMP) was orally administered in gelatin capsules at 0/0, 0/60, 25/15, 50/30 or 100/60 mg/kg (0/0, 0/27.3, 11.4/6.8, 22.7/13.6 or 45/27.3 mg/lb)b.w./dog to evaluate the effect of prolonged administration of Primor (5:1 SMD/OMP), and the potentiator ormetoprim, per se. The 5:3 dosing regimen used in this study provided a more severe ormetoprim challenge than would be experienced by dogs medicated with the 5:1 dosing regimen provided by Primor. The total active drug level used in this study

was approximately 1.5x, 3x and 6x the recommended Primor use level. For each component (i.e., SDM/OMP), the study levels were approximately 0/11x, 1/3x, 2/5x and 4/11x their recommended use levels. Four dogs (two male, two female) were assigned to each treatment group.

Ormetoprim at 60 mg/kg alone or in combination with 1000 mg sulfadimethoxine produced toxic reactions characterized by gastrointestinal disturbances and weight loss, brief seizures, hyperactivity and muscle tremors and salivation. Effects on hemopoiesis per se were not observed but elevations in hematocrit and hemoglobin, indicative of dehydration, were observed.

Three of the dogs on the high level of SDM/OMP and one on OMP per se were taken off medication during the fifth week. One SDM/OMP dog died during the sixth week, the other two and the OMP treatment dog, aided by 5% glucose administration, appeared normal in four to five weeks. Subsequently, they were placed back on medication during the ninth week at 75 mg SDM/45 mg OMP and 45 mg OMP/kg, respectively, without any adverse effects. Medication of another OMP treatment dog was discontinued during the eleventh week.

Results of this study indicate that concurrent medication with ormetoprim does not increase the toxicity of sulfadimethoxine. Also, inadvertent short term overdosing with Primor, or prolonged administration of label dose, will not have any significant adverse effects on dogs (Dr. R.E. Bagdon, Hoffmann-La Roche Inc.).

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 not 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

Data submitted in support of this NADA comply with the requirements of Section 512 of the Act and Section 512.11 of the implementing regulations. The data demonstrated that Primor tablets, when used under approved conditions of use, are safe and effective.

The drug is restricted to use by or on the order of a licensed veterinarian because a veterinarian is needed for the diagnosis of the underlying causes of bacterial infection for which the drug is indicated. Skin infections are often secondary to other underlying clinical conditions; allergic, dietary, hormonal, immunologic and metabolic. For the antibacterial to be effective, it should be used in conjunction with the treatment for the primary underlying clinical condition(s). Diagnosis of the primary underlying condition(s) requires the expertise of medically trained individuals with the aid of diagnostic facilities available to them. Therefore, the label for Primor tablets must bear the prescription legend.

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.