Date of Approval: July 22, 2004

FREEDOM OF INFORMATION SUMMARY

NADA 141-232

SIMPLICEF tablets

cefpodoxime proxetil

For the treatment of skin infections (wounds and abscesses) in dogs caused by susceptible strains of *Staphylococcus intermedius*, *Staphylococcus aureus*, *Streptococcus canis* (group G, β hemolytic), *Escherichia coli*, *Pasteurella multocida*, and *Proteus mirabilis*.

Sponsored by:

Pharmacia & Upjohn Co.

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1. GENERAL INFORMATION:

a.	File Number:	NADA 141-232
b.	Sponsor:	Pharmacia & Upjohn Co. 7000 Portage Rd. Kalamazoo, MI 49001-0199 Drug Labeler Code: 000009
c.	Established Name:	cefpodoxime proxetil
d.	Proprietary Name:	SIMPLICEF
e.	Dosage Form:	Film-coated tablets
f.	How Supplied:	SIMPLICEF tablets are supplied in the following strengths: 100 mg (scored, reddish orange, elliptical) in 100 count bottles 200 mg (light orange, elliptical) in 100 count bottles
g.	How Dispensed:	Rx
h.	Amount of Active Ingredients:	100 mg or 200 mg of active cefpodoxime per tablet
i.	Route of Administration:	Oral
j.	Species/Class:	Canine
k.	Recommended Dosage:	The dose range of SIMPLICEF (cefpodoxime proxetil) tablets is 5-10 mg/kg (2.3-4.5 mg/lb) body weight, administered orally, once a day for 5 to 7 days, or for 2 to 3 days beyond the cessation of clinical signs, up to a maximum of 28 days.
l.	Pharmacological Category:	Antimicrobial
m.	Indications:	For the treatment of skin infections (wounds and abscesses) in dogs caused by susceptible strains of *Staphylococcus intermedius, Staphylococcus aureus, Streptococcus canis* (group G, β hemolytic), *Escherichia coli, Pasteurella multocida,* and *Proteus mirabilis.*

2. EFFECTIVENESS:

a. Dosage Characterization:

(1) In an initial pharmacokinetic study (**Royer 1990**, Study # 7256-90-084), cefpodoxime plasma concentrations after a single daily dose of 7 mg/kg were compared to a minimum inhibitory concentration target level of 0.5 mcg/mL, typical for proposed label pathogens. This study demonstrated that plasma concentrations remained above the MIC target value for 24 hours after a single daily dose of 7 mg/kg body weight, suggesting a once daily dose. To further define the daily dose level, a skin infection model study was undertaken to evaluate the effectiveness of cefpodoxime proxetil at once daily doses of 5 and 10 mg/kg in dogs with surgically induced infected wounds.

(2) Soft Tissue Infection Model:

(a) Study Title and Number: "Preliminary Study of Various Dosage Regimens of Cefpodoxime Proxetil in an Infected Surgical Wound Model in the Dog." Study # 0852-7926-2002-01

(b) Type of Study: Effectiveness laboratory study

(c) Date: February 5, 2003

(d) Investigator and Location: Dr. John Berg, College of Veterinary Medicine, University of Missouri, Columbia, MO

(e) General Design:

1 Purpose: The objective of this study was to evaluate the effectiveness of once daily oral administration of cefpodoxime proxetil at doses of 5 mg/kg and 10 mg/kg body weight in the treatment of surgically induced skin infections in dogs. In addition, the effectiveness of cefpodoxime proxetil was compared to the effectiveness of amoxicillin/clavulanic acid when administered orally, twice daily in the treatment of surgically induced infected wounds.

2 Test Animals: A total of 50 dogs were used in this study, ten dogs per treatment group.

3 Dosage Groups: Treatment group 1, the negative control group, received a once daily oral dose of UNIPET NUTRITABS. Treatment groups 2 and 3 received a once daily oral dose of cefpodoxime proxetil (100 mg cefpodoxime equivalents per tablet) at a dose of 5 and 10 mg cefpodoxime equivalents/kg body weight, respectively, and were treated for five consecutive days. The fourth treatment group, the active control

group, was administered amoxicillin/clavulanic acid at a dose of 13.75 mg/kg body weight, administered twice per day for five consecutive days.

4 Measurements and Observations: Two wounds were surgically prepared and inoculated with *Escherichia coli* and *Staphylococcus intermedius*. Lesions were cultured on Days 1, 2, 3, 4, 6, 9, and 13.

5 Statistical Analysis: The areas under the curves (AUC) for the number of colony forming units (CFUs) for *E. coli* and for *S. intermedius* were the primary decision parameters and were statistically analyzed.

(f) Results: The 5 mg/kg and 10 mg/kg treatment groups both produced a statistically significant reduction in bacterial counts of both pathogens at the site of infection compared to the negative control group ($p \leq 0.001$).

(g) Conclusions: Cefpodoxime proxetil at doses of 5 mg/kg and 10 mg/kg body weight administered once daily are both significantly better than placebo in reducing bacterial counts in surgically induced skin infections.

b. Substantial Evidence:

(1) PHARMACOKINETIC STUDY:

The following laboratory study was conducted to further define the pharmacokinetics of cefpodoxime in dogs and to establish the therapeutic equivalency between SIMPLICEF tablets and oral suspension.

(a) Study Title and Number: "Pharmacokinetic Comparison of Cefpodoxime Proxetil Tablets (100 mg/dog) and Suspension (10 mg/kg BW) in Dogs after a Single Dose Administered Orally" Study # 7926-2001-0384

(b) Type of Study: Pharmacokinetic laboratory study

(c) Date: February, 2003

(d) Investigators: Brown, S.A., Modric, S., Pharmacia & Upjohn

(e) General Design:

1 Purpose: To compare pharmacokinetic properties of two clinical formulations of cefpodoxime proxetil, tablets and suspension, after a single dose of 10 mg cefpodoxime equivalents/kg body weight administered orally to Beagle dogs and to determine whether the two formulations are bioequivalent.

2 Dosage Groups: A 2-way crossover study in Beagle dogs (n = 12) comparing pharmacokinetic properties of cefpodoxime proxetil tablet and suspension formulations, with a 1-week washout period between the two treatment periods.

3 Measurements and Observations: Blood samples were collected prior to each drug administration, and at the following time points after drug administration: 0.5, 1, 1.5, 2, 2.5, 3, 5, 8, 12, 16, 24, 36, and 48 hours. For determination of bioequivalence between the tablet and suspension formulations, pharmacokinetic analysis included determination of $AUC_{0\text{-}LOQ}$ [area under the curve (AUC) from time zero to the last concentration above the limit of quantitation (LOQ)] and observed C_{max} [maximum observed plasma concentration] for each of the two formulations.

(f) Results:

Table 1. Summary of Pharmacokinetic Parameters Obtained After a Single Oral Dose of 10 mg Cefpodoxime/kg Body Weight, Administered Either as a Tablet or an Oral Suspension

PK Parameter	Unit	Suspension (SD)	Suspension dose-norm. (SD)	Tablet (SD)	Tablet dose-norm. (SD)
$AUC_{0\text{-}\infty}$	mcg•hr/mL	148 (43.1)	164 (54)	145 (77.6)	161 (72)
$AUC_{0\text{-}LOQ}$	mcg•hr/mL	144 (43.5)	162 (48.6)	142 (77.5)	156 (76.1)
C_{max}	mcg/mL	17.8 (5.5)	20.1 (6.20)	16.4 (11.8)	17.8 (11.4)
$t_{1/2,z}$	hr	6 (3.01)	-	5.61 (1.15)	-
t_{max}	hr	2 (0.564)	-	2.21 (0.542)	-
$MRT_{0\text{-}\infty}$	hr	7.92 (1.26)	-	9.21 (1.97)	-

$t_{1/2,z}$ – terminal elimination half life
t_{max} – time of maximum concentration
MRT – mean residence time
SD – standard deviation

(g) Conclusion: The mean treatment differences in $AUC_{0\text{-}LOQ}$ and C_{max} did not exceed the limit of ±10% and ±15%, respectively, suggesting that the two formulations of cefpodoxime proxetil, when administered as a single dose of 10 mg cefpodoxime equivalents/kg body weight in dogs were therapeutically equivalent.

(2) FIELD STUDY:

(a) Study Title and Number: "Clinical Effectiveness of 5 mg Cefpodoxime Proxetil / kg BW Given Once Daily for 5-7 Days Compared to a Positive

Control Drug Given Twice Daily for 5-7 Days as Treatment for Canine Skin and Soft Tissue Infections" Study # 0852-8625-2002-001

(b) Type of Study: Effectiveness Field Study

(c) Study Dates: January 2002 – July 2002

(d) Locations and Investigators:

James Powell, D.V.M. New Port Richey, FL	Brian Scott, D.V.M. Lake Mary, FL
Randall Carpenter, D.V.M. Greenville, MI	David Visser, D.V.M. South Bend, IN
Marc Leven, D.V.M. Wyoming, MI	Philip VanVranken, D.V.M. Battle Creek, MI
Mark Lapierre, D.V.M. Greensboro, NC	Joseph Kinnarney, D.V.M. Reidsville, NC
Haskell Wright, D.V.M. Glendale, AZ	Joseph Hauptman, D.V.M., Ph.D. East Lansing, MI
Donald Schlange, D.V.M. Antioch, CA	Debra Nelson, D.V.M. Casa Grande, AZ
Samuel Geller, D.V.M. Quakertown, PA	James Matteson, D.V.M. Tracy, CA
Timothy Patterson, D.V.M. Bristol, PA	David Lukof, D.V.M. Harleysville, PA
Terry Clekis, D.V.M. St. Petersburg, FL	Hunter Wilcox, D.V.M. Cherry Hill, NJ
Samuel Griffin, D.V.M. Albemarle, NC	Donald Heagren, D.V.M. Durham, NC
Brett Berryhill, D.V.M. Baton Rouge, LA	Thomas Greene, D.V.M. Livonia, LA
Lynn Buzhardt Zachary, LA	

(e) General Design

1 Purpose of Study: To confirm the effectiveness and safety of cefpodoxime proxetil for the treatment of canine skin infections (wounds and abscesses) when administered orally at 5 mg cefpodoxime / kg body weight once daily for 5-7 days compared to an active control of 13.75 mg amoxicillin/clavulanic acid / kg body weight twice daily for 5-7 days.

2 Description of Test Animals: Two hundred and sixteen (216) dogs with infected wounds and/or abscesses. These included dogs of all ages, both sexes, and many different breeds and mixes.

3 Control and Treatment Groups:

Table 2. Treatment Groups

Tx Group	Dose mg/kg	Number of Animals Enrolled (evaluable)
I	cefpodoxime 5 mg/kg SID for 5-7 days	118 (106)
II	amoxicillin/clavulanic acid 13.75 mg/kg BID for 5-7 days	98 (86)
total		216 (192)

4 Inclusion Criteria: Presence of an observable wound or abscess that was likely to be infected. The wound or abscess may have resulted from, but was not limited to, a laceration, puncture, bite wound, crushing injury, or surgery. The lesion may have been acute or chronic. To be included in the statistical analysis, the wound/abscess had to culture positive for one or more bacterial organisms.

5 Exclusion Criteria:
- i Wounds without signs of infection (e.g., pus).
- ii Pyoderma as the primary lesion.
- iii Dogs with secondary metabolic conditions were not excluded unless the investigator deemed it so severe that normal wound healing would be affected.
- iv Systemic or topical antibiotics or short-acting corticosteroid within two weeks or long-acting (depo) corticosteroids within 30 days of enrollment.

6 Dosage Form:

cefpodoxime
- i 100 mg tablets
- ii 200 mg tablets
- iii oral suspension (100 mg/5 mL)

amoxicillin/clavulanic acid
- i 62.5 mg tablets
- ii 125 mg tablets
- iii 250 mg tablets
- iv 375 mg tablets
- v oral suspension (62.5 mg/mL)

7 Drug Administration:

i Dosage amount, frequency, and duration:
cefpodoxime: 5 mg/kg (tablets or liquid) once daily for 5-7 days.
amoxicillin/clavulanic acid: 13.75 mg/kg (tablets or liquid) twice daily for 5-7 days.

ii Route of administration: oral

iii Other comments: As noted above, animals could be dosed with either tablets or liquid. This decision was based on their weights with the smaller dogs receiving suspension and the larger dogs receiving tablets. Of the 106 evaluable cefpodoxime cases, 24 were dosed with oral suspension. Of the 86 evaluable amoxicillin/clavulanic acid cases, nine were dosed with oral suspension.

8 Variables Measured:

Infection Criteria:
i At the initial and final examinations, is there a purulent exudate present?
ii At the initial and final examinations, each inflammation measure (pain, swelling, redness, heat) was scored: 0=none, 1=mild/moderate, 2=severe.
iii At the final examination, was further antimicrobial treatment needed?

Wound Healing Criteria:
At the final examination, is the lesion completely healed or healing at a normal rate?

Aerobic bacterial cultures were collected from all dogs pre-treatment and from the clinical failures that still displayed a purulent exudate post-treatment.

Follow-up examinations or phone calls were conducted 7-11 days after the final examination to determine if the infection had relapsed.

9 Criteria for Success/Failure: The primary variable was the clinical cure rate. A clinical cure decision was determined at the final exam as:

i No purulent exudate, and
ii None of the inflammation measures could have gotten worse, and
iii If the sum of all inflammation measures at the initial exam was greater than 1 then the same sum at the final exam must have decreased, and

iv No further antimicrobial treatment was needed, and
v The lesion must be completely healed or healing at a normal rate, and
vi The case must not relapse.

A secondary variable, described as the veterinary cure rate, recorded the investigating veterinarian's overall impression of how well the treatment worked.

(f) Results:

The objective of the statistical analysis was to test the non-inferiority of cefpodoxime against the active control, (amoxicillin/clavulanic acid tablets or liquid). The one-sided test was conducted using the lower limit of a 90% confidence interval on the difference between the estimated cure rates.

Table 3. Clinical and Veterinarian Cure Rates by Treatment Group

Variable	cefpodoxime		amoxicillin/clavulanic acid		Difference (std. error)	90% Confidence Interval*
	#Cure/Total	%	#Cure/Total	%		
Clinical Cure	94/106	88.7%	76/86	88.4%	0.3% (4.6)	(-7.3%, 8.4%)
Veterinarian Cure	101/106	95.3%	79/86	91.9%	3.4% (3.5)	(-2.5%, 10.2%)

* If the lower limit of 90% confidence interval is greater than -15%, then cefpodoxime is statistically non-inferior to amoxicillin/clavulanic acid.

The clinical cure rate difference between the tested drug (cefpodoxime, 88.7%) and the active control (amoxicillin/clavulanic acid, 88.4%) was 0.3% and the lower limit of the 90% confidence interval was -7.3%. This lower confidence limit was above the delta, non-inferiority margin, of -15%.

The veterinarian cure rate difference between the tested drug (cefpodoxime, 95.3%) and the active control (amoxicillin/clavulanic acid, 91.9%) was 3.4% and the lower limit of the 90% confidence interval was -2.5%. This lower confidence limit was above the delta, non-inferiority margin, of -15%.

No statistical differences ($p > 0.05$) in either clinical or veterinarian cure rates between dogs fasted for at least five doses and fed dogs were found. Fasted is defined as not dosed within two hours of a meal.

Table 4. Fed vs. Fasted Effect: Dogs on Cefpodoxime

	Not fasted ≥ 5 doses	Fasted ≥ 5 doses
Clinical Cure	64/71 (90.1%)	30/35 (85.7%)
Veterinarian Cure	67/71 (94.4%)	34/35 (97.1%)

(g) Adverse Reactions: A total of 216 dogs of various breeds and all ages were included in the field study safety analysis. The following table shows the number of dogs displaying each clinical observation.

Table 5. Abnormal Health Findings in the U.S. Field Study[1]

Clinical Observation	**cefpodoxime** (n=118)	**amoxicillin/clavulanic acid** (n=98)
Vomiting	2	4
Diarrhea	1	1
Increased water drinking	0	2
Decreased appetite	1	1

[1] Dogs may have experienced more than one of the observations during the study.

(h) Microbiology: Cefpodoxime has a broad spectrum of clinically useful antibacterial activity that includes staphylococci, streptococci, and gram-negative species (including *Pasteurella*, *Escherichia,* and *Proteus*). The compound is not active against most obligate anaerobes, *Pseudomonas* spp., or enterococci. The minimum inhibitory concentrations (MICs) for cefpodoxime against gram-positive and gram-negative pathogens isolated from canine skin infections (wounds and abscesses) in a 2002 U.S. field study are presented in Table 6. All MICs were determined in accordance with the National Committee for Clinical Laboratory Standards (NCCLS). Appropriate quality control (QC) ranges for *in vitro* susceptibility testing are presented in Table 7.

Table 6. Cefpodoxime Minimum Inhibitory Concentration Values (mcg/mL) from a 2002 Field Study Evaluating Skin Infections (wounds and abscesses) of Canines in the United States.

Organism Name	**No. tested**	**MIC_{50}**	**MIC_{90}**	**Range**
Escherichia coli	41	0.25	0.50	0.12- >32.0
Pasteurella multocida	32	≤0.03	≤0.03	≤0.03-0.12
Proteus mirabilis	14	≤0.03	0.06	≤0.03-0.06
Staphylococcus aureus	19	2.0	2.0	0.12-2.0
Staphylococcus intermedius	118	0.12	0.50	0.12->32.0
Streptococcus canis (group G, β hemolytic)	33	≤0.03	≤0.03	≤0.03†

†No Range, all isolates yielded the same value.

Table 7. Acceptable Ranges for Quality Control Strains for Cefpodoxime

QC ATCC strain	KB Disk Diffusion Method[a]		Broth Micro-dilution Method[a]
	Drug concentration	Zone diameter	MIC
Escherichia coli 25922	10 mcg	23-28 mm	0.25-1 mcg/ml
Staphylococcus aureus 25923	10 mcg	19-25 mm	
Staphylococcus aureus 29213			1-8 mcg/ml

[a] These ranges are for non-fastidious organisms using cation-adjusted Mueller-Hinton agar or broth medium. The dilution range should encompass the QC ranges of these strains in the broth micro-dilution method. When susceptibility testing is performed for streptococci, *Streptococcus pneumoniae* ATCC 49619 should be included as a QC strain in the presence of 5% lysed sheep blood. However, at the time of this study no QC ranges of *S. pneumoniae* for cefpodoxime were established by the NCCLS. The current established QC ranges of *S. pneumoniae* established by NCCLS are reflected in the labeling of this product.

(i) Conclusions: Cefpodoxime was shown to be safe and effective in this multi-center field study. The study demonstrated that SIMPLICEF tablets and oral suspension were considered noninferior to the comparator product (amoxicillin/clavulanic acid tablets and liquid) in the treatment of canine skin infections (wounds and abscesses) caused by susceptible strains of *Staphylococcus intermedius, Staphylococcus aureus, Streptococcus canis* (group G, β hemolytic), *Escherichia coli, Pasteurella multocida,* and *Proteus mirabilis*.

(3) PHARMACOKINETIC / PHARMACODYNAMIC CONFIRMATION OF DOSE EFFECTIVENESS

(a) Pharmacokinetic Dataset: The data used in this evaluation was obtained from the investigation titled "Pharmacokinetic Comparison of Cefpodoxime Proxetil Tablets (100 mg/dog) and Suspension (10 mg/kg BW) in Dogs after a Single Dose Administered Orally" Study # 7926-2001-0384 (refer to page 3)

(b) Effectiveness Criteria: The most recent National Committee for Clinical Laboratory Standards (NCCLS) breakpoints incorporate pharmacodynamic information, where the standard dosing for β-lactams results in free serum drug concentrations exceeding pathogen MIC_{90} values for at least 40% of the dosing interval[1]. In the case of β-lactams, studies in human patients have demonstrated that when free drug T>MIC is 40% - 50% of the dosing interval, the likelihood of treatment success is >80%[2]. The criteria are dependent upon

[1] Craig W (2002). Pharmacodynamics of antimicrobials: general concepts and applications. In: *Antimicrobial Pharmacodynamics in Theory and Clinical Practice*. Nightingale, Murakawa and Ambrose, Eds., Marcel Dekker, New York, pp 1-22.
[2] Peric, et al., (2003). *Clinical Therapeutics*, 25, 169-177.

the ability of the free drug concentrations to accurately predict active drug concentrations at the site of the infection.

Using this information for the current application, and knowing that the highest MIC_{90} values are associated with *Staphylococcus aureus* (MIC_{90} = 2.0 mcg/mL), the criteria for this pharmacokinetic/pharmacodynamic analysis of cefpodoxime tablets and oral suspension in dogs, is T>2 mcg/mL $\geq$8 hrs.

(c) Data Analysis: Free drug concentrations for the tablet and for the suspension (values normalized within each subject to concentrations expected with an exact dose of 10-mg/kg) were estimated based on the proportion of unbound drug in humans: ranging from 78% to 67% in serum and from 79% to 71% in plasma[3]. Using this information, the dose-normalized total plasma cefpodoxime concentrations of each individual were adjusted by multiplication of the total drug concentrations by a factor of 0.70.

The total time that free drug concentrations exceeded 2 mcg/mL was estimated by extrapolating the time for these estimated free concentrations to decrease from the last free plasma drug concentration exceeding 2 mcg/mL to a value of 2 mcg/mL (ΔT). Model-derived estimates of T>2 mcg/mL were not used to avoid potential bias associated with model misspecification. Estimates were based upon the following equation:

$$\Delta T = Ln(Ct/2 \text{ mcg/mL})/\lambda z$$

where Ct = last "observed" free concentration exceeding 2 mcg/mL, and λz is the estimated terminal elimination rate constant (using noncompartmental procedures in WinNonLin). Values for ΔT are then added to the times associated with Ct to determine T>2 mcg/mL.

(d) Results: The results of this analysis for both tablet and suspension formulations are provided in Table 8.

[3] Physician's Desk Reference, 2003: VANTIN Tablets and Oral Suspension

Table 8: Time Above 2-mcg/mL (hrs) of Estimated Free Cefpodoxime Concentrations for Tablet and Suspension SIMPLECEF Formulations in Dogs

Tablet	Suspension
19.5	12.4
11.6	14.5
14.6	15.7
14.0	10.5
8.0	17.2
17.5	17.3
12.5	14.1
13.9	13.9
15.8	13.0
15.1	14.9
20.6	16.4
7.6	11.5

Of the twelve subjects administered the tablet, one dog had a T > 2 mcg/mL estimate that was 20 minutes short of the targeted eight hour duration. We conclude that this deviation is not inconsistent with effectiveness since it is well within the limits of normal experimental error. With the suspension, all 12 subjects had free serum drug concentrations exceeding 2 mcg/mL for more than eight hours. We also note that this study was conducted under fasted condition. Food results in a slight increase in drug bioavailability for both the tablet (1.33 * fasted serum drug concentrations, estimated in humans) and suspension (1.11 * fasted serum drug concentrations, values estimated in humans). If given with food, these estimates of T > 2 mcg/mL will increase rather than decrease.

(e) Conclusion: From a PK-PD perspective, the microbiological data submitted for cefpodoxime tablets and oral suspension supports the findings of the field study.

(4) DISSOLUTION STUDY: BRIDGING THE VANTIN FORMULATION USED IN FIELD STUDY TO THE FINAL MARKET FORMULATION (SIMPLICEF).

(a) Background: The purposes of the *in vitro* dissolution data are:

1 To provide a bridge between the VANTIN tablets used in the field study and the proposed market formulation for dogs (SIMPLICEF).

2 To demonstrate that splitting the 100-mg SIMPLICEF tablet at the score does not alter the rate or extent of cefpodoxime absorption.

(b) Protocol:

1 The following comparisons supported the two study objectives: SIMPLICEF 100-mg scored tablets versus VANTIN 100-mg tablets, SIMPLICEF 200-mg tablets versus VANTIN 200-mg tablets, and SIMPLICEF 100-mg tablets broken versus SIMPLICEF 100-mg tablets intact. For the broken tablets, one half-tablet was tested per vessel. For the whole tablet, the percent dissolved reflects the ability to achieve the target of 100 mg drug released into the dissolution medium. For the half-tablet, the percent dissolved reflects the release based upon an estimated 50 mg available per vessel.

2 There were twelve vessels per treatment. To confirm comparable *in vitro* dissolution rates, products were required to demonstrate greater than 85% dissolution within 30 minutes. Should that occur, the products were concluded to be similar, and no additional mathematical evaluation would be required. To ensure the content uniformity of the scored tablets, the broken tablets are required to meet the USP acceptance criteria for uniformity of dosage form, using weight variation as described in General Chapter <905>.

(c) Results:

1 The *in vitro* dissolution tests confirm that VANTIN and SIMPLICEF dissolve at a similar rate and to a similar extent. Within each lot, the twelve individual tablets exhibited greater than 85% dissolved within 15 minutes, exceeding the dissolution rate targeted in the acceptance criteria. By 30 minutes of testing, the tablets consistently showed greater than 90% dissolution.

2 The potency of the halved tablets ranged from 92.1% to 106.1% of targeted values (mean = 99.4%, RSD = 2.9).

(d) Conclusions:

1 The effectiveness testing conducted in dogs using the VANTIN tablets can be used to support product effectiveness for the revised formulation, SIMPLICEF 100-mg and 200-mg strength tablets.

2 Splitting the 100-mg SIMPLICEF tablet at the score does not alter the rate or extent of cefpodoxime absorption or the amount of drug being delivered.

3. TARGET ANIMAL SAFETY:

a. Toxicity and Tolerance Studies:

(1) Combined Toxicity and Tolerance Study in Adult Dogs:

(a) Study Title and Number: "U-76,252: Thirteen Week Oral Toxicity Study in Beagle Dogs." Study Report # 7263-87-034

(b) Type of Study: Target Animal Safety: toxicity/tolerance study at 0-2.5-10x (based on 10 mg/kg) in young adult dogs.

(c) Study Dates: 1985

(d) Location and Investigator: Conducted by the Sankyo, Co. in Japan. Masahiro Mori, Ph.D. was the study director.

(e) General Design:

1 Purpose of Study: To provide information on the toxic effects of PNU-76252 following oral administration in Beagle dogs at doses up to 100 mg/kg/day for 13 weeks. This study was conducted and inspected according to GLP regulations.

2 Description of Test Animals: 12 male and 12 female Beagle dogs 10-14 months old.

3 Control and Treatment Groups: The 24 animals were allocated into 4 replicates of 6 dogs each (3 males and 3 females). This allowed for 2 dogs (1 male and 1 female) of each treatment group in each replicate.

Table 9. Treatment Groups

Tx Group	n	Male	Female
0 mg/kg (0x)	8	4	4
25 mg/kg (2.5x)	8	4	4
100 mg/kg (10x)	8	4	4

4 Dosage Form: Bulk drug in capsules

5 Drug Administration:

i Dosage amount, frequency, and duration: 0, 25, 100 mg/kg bulk cefpodoxime was administered once daily for 13 consecutive weeks (91 days).

ii Route of administration: orally by gelatin capsules.

6 Variables Measured: General observations twice daily, body weight weekly, food intake daily, water intake and urine volume daily, urinalysis at Weeks -3, -1, 6, and 13, fecal occult blood at Weeks -3, -1, 6, and 13, hematology at Weeks -2, -1, 4, 8, and 12, serum biochemistry at Weeks -2, -1, 4, 8, and 12, liver function testing (BSP) at Weeks -2 and 11, kidney function testing (PSP) at Weeks -2 and 11, electrocardiography at Weeks -3 and 11, ophthalmoscopic examination at Weeks -2 and 11, electroretinography (left eye) at Weeks -2 and 12, reflex function test at Weeks -3 and 13, gross pathological exam and organ weights 24 hours after last dosing, and histopathological exam of all major organ tissues.

(e) Results:

1 Clinical Observations and Physical Exams: No observable effect except for white material noted in the feces of the 100 mg/kg group which was considered to be unabsorbed drug.

2 Clinical Pathology: None of the statistically significant differences found between treatment groups or over time within treatment groups are considered clinically relevant; however, a discussion of some of these significant findings is presented below.

As a class, cephalosporins are known to be capable of causing blood dyscrasias, including neutropenia. In this study, only two of the hematology variables demonstrated significant differences between treatment groups. For activated partial thromboplastin time (APTT), the 25 and 100 mg/kg groups were actually faster than the control group, which is counter-indicative to a clotting function problem. There was also a statistically significant difference noted by dose and by time for platelets. The dose group of 100 mg/kg/day was significantly decreased in platelets (PLT) as compared to the control group at weeks 8 and 12 (all $p < 0.01$) and the dose group of 25 mg/kg/day was also decreased in platelets at weeks 4, 8, and 12 ($p < 0.1$). However, all treated group means were in the normal range.

For alanine aminotransferase (ALT), there were significant differences among the three dose groups ($p < 0.05$) and the dose and week interaction ($p < 0.05$). There were significant increases for the 100 mg/kg/day group at weeks 4 and 8 and for the 25 mg/kg/day group at week 8 as compared to the control group (all $p < 0.05$). However, all treated group means were in the normal range.

For protein (PRO), there was a significant difference among the three dose groups ($p < 0.05$). There were significant decreases for 25 and 100 mg/kg/day groups as compared to the control group (both $p < 0.05$). However, all individual treated dogs' serum protein values were in the normal range.

3 Pathology: No clinically relevant abnormalities were noted.

(f) Conclusions: The statistically significant differences were not considered to be toxicologically significant and not to have clinical relevance because they were sporadic, were not dose-dependent and were within the range of background changes noted in the laboratory where the study was conducted.

(2) Drug Tolerance Study in Puppies:

(a) Study Title and Number: "U-76,252: One Month Oral Toxicity Study in Infant Dogs" Study # 7227-89-078

(b) Type of Study: Target Animal Safety: Drug tolerance study at 0-10x (based on 10 mg/kg) in puppies.

(c) Study Dates: 1987

(d) Location and Investigator: Conducted by the Sankyo Company Ltd, Fukuroi City, Shizuoka Prefecture, Japan. Masahiro Mori, Ph.D. was the study director.

(e) General Design:

1 Purpose of Study: The objective of this study was to provide information on the toxic effects of PNU-76252 following oral administration in Beagle puppies at doses up to 100 mg/kg/day for 4 weeks. This study was conducted and inspected according to GLP regulations.

2 Description of Test Animals: six male and six female Beagle puppies approximately three weeks old.

3 Control and Treatment Groups: The 12 animals were allocated into 3 replicates of 4 dogs each (2 males and 2 females). This allowed for 2 dogs (1 male and 1 female) of each treatment group in each replicate.

Table 10. Treatment Groups

Tx Group	n	Male	Female
0 mg/kg (0x)	6	3	3
100 mg/kg (10x)	6	3	3

4 Dosage Form: Bulk drug in capsules

5 Drug Administration:

i Dosage amount, frequency, and duration: 0 and 100 mg/kg bulk cefpodoxime was administered once daily for 28 consecutive days.

ii Route of administration: orally by gelatin capsules

6 Variables Measured: General observations twice daily, body weight approximately every other day, food intake daily, hematology at Days -1, 14, and 28, serum biochemistry at Days -1, 14, and 28, gross pathological exam and organ weights 24 hours after last dosing, and histopathological exam of all major organ tissues.

(f) Results:

1 Clinical Observations and Physical Exams: No observable effect except for white material noted in the feces of the 100 mg/kg group which was considered to be unabsorbed drug.

2 Clinical Pathology: There were no statistically significant differences noted among variables in the hematology or serum biochemistry data analyses in this study.

3 Pathology: No clinically relevant abnormalities were noted.

(g) Conclusions: No treatment related effects were observed, except for unabsorbed drug in the feces, when PNU-76252 (bulk cefpodoxime) was given to Beagle puppies orally for 28 consecutive days, at a dose of 100 mg/kg.

(3) Pharmacokinetic Bridge: Bulk Drug (TAS dosage form) vs. Final Formulation

Since the TAS data were generated with a non-final formulation, it was necessary to develop a pharmacokinetic bridge between the dosage form used in the TAS study and the final formulation intended for use in dogs. Because the bulk capsule formulation was no longer available, at least part of the comparison needed to be based upon previously collected pharmacokinetic data. Therefore, it was necessary to assess the potential inter-study variability that might bias the relative bioavailability comparison. The assessment of inter-occasion differences in drug pharmacokinetics was obtained by comparing contemporarily generated pharmacokinetic profiles following intravenous (IV) cefpodoxime administration to existing IV datasets. In addition, since the human AUC values observed with

the tablet and suspension increased by 33% and 11%, respectively, when administered with food[4,5], the canine tablet and suspension AUC values were likewise multiplied by 1.33 and 1.11 respectively, to insure safety under both fed and fasted conditions.

Based upon the clinical TAS studies conducted using the bulk drug in capsules, the margin of safety for the oral suspension and tablet was estimated as follows:

$AUC_{0\text{-}inf}$ bulk drug/$AUC_{0\text{-}inf}$ mean IV = F bulk drug
$AUC_{0\text{-}inf}$ tablet$AUC_{0\text{-}inf}$ mean IV = F tablet* 1.33 = corrected F tablet
$AUC_{0\text{-}inf}$ suspension/$AUC_{0\text{-}inf}$ mean IV = F suspension* 1.11 = corrected F suspension

Margin of safety tablet = Safety study margin * corrected F tablet/ F bulk drug
Margin of safety suspension = Safety study margin * corrected F suspension/ F bulk drug

(a) "Plasma levels of U-76,252 in dogs during a subacute toxicity test after oral administration of U-76,252." Study # 7256-88-004

1 Investigators: Sasahara K, Sekine M, Tarumi C, Mori M, Laboratory Animal Science & Toxicology Laboratories, Sankyo Company Ltd, Fukuroi City, Shizuoka Prefecture, Japan.

2 Purpose: To determine plasma cefpodoxime concentrations achieved on the first and final day of dosing in the 13-week oral toxicity study in dogs. The toxicity portion of the study was conducted according to GLPs; however this portion of the study was conducted as a non-GLP study.

3 Test Animals: A total of 32 Beagle dogs (16 male and 16 female) were used in this study. Animals ranged from 10 to 14 months of age at dose initiation. Body weights of the dogs ranged from 8.1 to 10.6 kg and 8.0 to 9.8 kg for males and females, respectively. Dogs were divided into four groups, each group consisting of four males and four females. Siblings were not included in the same group. Blood samples for analysis were collected from 12 male dogs (four from each of the groups that received PNU-76252 treatment).

4 Dosage Form: Bulk drug was administered in gelatin capsules.

[4] Borin and Forbes (1995). Effect of food on absorption of cefpodoxime proxetil oral suspension in adults. Antimicrobial Agents and Chemotherapy, 39: 273-275.

[5] Physician's Desk Reference 2003: VANTIN Tablets and Oral Suspension

5 Dosages Used, Route of Administration, and Test Duration: Dogs received a single daily oral dose of 0 (empty capsules), 25, 100 or 400 mg/kg/day PNU-76252 each morning immediately prior to feeding for 4 weeks.

6 Pertinent Variables Measured: Blood samples were collected at 0.5, 1, 2, 3, 4, 6, 8, and 24 hours after drug administration on the first day of dosing. Samples were also collected 0, 0.5, 1, 2, 3, 4, 6, 8, and 24 hours after drug administration on the last day of dosing. Samples were analyzed for PNU-76253 (cefpodoxime) by HPLC.

7 Results:

The pivotal pharmacokinetic variables were determined both on the basis of observed drug concentrations and as the variable value divided by the administered dose. The results are summarized in Table 11. It should be noted that while the AUC value estimated from 0-last represents a partial AUC for Day 0, it represents $AUC_{0\text{-inf}}$ for Day last. Therefore, the Day last values were compared to the canine $AUC_{0\text{-inf}}$ values observed following a single administration of the tablet or oral suspension.

Table 11. Dose Linearity Study: Bulk Drug in Capsule: Mean Data

Dose	Day	$AUC_{0\text{-last}}$ (mcg*hr/mL)	$AUC_{0\text{-last}}$ /dose	Cmax (mcg/mL)	Cmax/dose	Tmax (hr)
		Mean (%CV)				
25	0	190.53 (54)	7.62	28.28 (30)	1.13	3.50 (55)
25	last	433.18 (13)	17.33	33.45 (22)	1.34	5.25 (42)
100	0	1109.29 (16)	11.09	99.80 (13)	1.00	4.50 (53)
100	last	1267.17 (13)	12.67	114.33 (11)	1.14	4.00 (50)
400	0	2225.30 (14)	5.56	147.80 (16)	0.37	3.75 (13)
400	last	2489.92 (9)	6.22	186.43 (7)	0.47	6.50 (15)

8 Conclusions: The rate and extent of absorption are linear up to at least 100 mg/kg (bulk drug), but are less than dose proportional at higher levels (e.g., 400 mg/kg). There is some accumulation over time, as indicated by the higher values observed after the final 13 week sample as compared to the first dosing day. For the most part, the magnitude of accumulation appears to be independent of dose (i.e., there do not appear to be any nonlinear elimination processes). Therefore, bioavailability comparisons (e.g., tablet vs. bulk drug) generated on the basis of a single dose should adequately reflect relative bioavailability differences that occur under steady state conditions.

(b) "The absolute bioavailability of U-76,252 in the dog: a comparison of tablets and an oral solution to an intravenous dose of U-76,253A." Study # 7256-90-084

1 Investigators: Royer ME, McCurdy VE, Walters RR, VandeGeissen TL, Jones BW, Pharmacia Corp., Kalamazoo MI.

2 Purpose: The purpose of this study was to assess the relative bioavailability of PNU-76252 (i.e., U-76,252; cefpodoxime proxetil) when administered as a tablet or an oral solution. This study was conducted as a non-GLP study.

3 Test Animals: A total of six male Beagle dogs were used in this study. Animals ranged from 12.4 to 15.9 kg; age was not specified. Doses were administered in a three-way crossover design with a one-week washout period between doses.

4 Dosage Form, Dosages Used, Route of Administration, and Test Duration: Doses were administered as: (A) an oral dose of PNU-76252 dissolved in 50 mL of 0.1M citric acid, 42.5% sucrose, and 3.3% v/v ethanol followed by 50 mL of water, (B) an oral dose of one tablet containing PNU-76252 followed by 50 mL of the above placebo formulation and 50 mL of water, and (C) an intravenous dose of PNU-76253A (i.e., U-76,253A; cefpodoxime sodium) in isotonic saline. All doses were equivalent to 100 mg of PNU-76253 (cefpodoxime moiety alone). Dogs received a single dose of each formulation in a three-way crossover design with a one-week washout period between doses.

5 Pertinent Variables Measured: Blood samples were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10.5, 14, and 24 hours after administration of the oral solution and tablet formulations. Blood samples were collected at 0, 0.08, 0.17, 0.5, 1, 2, 3, 5, 7, 10.5, 14, and 24 hours after administration of the intravenous formulations. Samples were analyzed for PNU-76253 (cefpodoxime moiety alone) by HPLC.

6 Results: Slight differences in pharmacokinetic values were noted, depending upon whether the data were analyzed with or without dose correction (correction for the actual amount received by dividing parameter by the administered mg/kg dose). Therefore, both the observed and corrected parameter estimates are provided in Table 12.

Table 12. Mean Pharmacokinetic Values for All Treatments Within Subjects

	$AUC_{0\text{-last}}$ (mcg*hr/mL)	$AUC_{0\text{-last}}$ /dose	$AUC_{0\text{-inf}}$ /dose	Cmax (mcg/mL)	Cmax /dose	Tmax (hr)	F – corrected for dose
solution	244.47 (15)	34.17 (11)	34.93	29.41 (13)	4.13 (16)	2 (16)	0.63 (6)
tab	259.32 (20)	34.14 (15)	34.71	30.00 (23)	3.96 (20)	2.67 (26)	0.63 (9)
IV	379.67 (14)	54.00 (10)	54.93				

The terminal elimination half-life of PNU-76253 in plasma was 4.8±0.3 hour. Based upon the IV dataset, the volume of distribution is consistent with a compound that distributes primarily into the interstitial fluid (Vdss ~ 0.11 L/kg). The total systemic clearance is ~0.018 L/hr/kg.

(c) "Pharmacokinetic Characterization of Cefpodoxime Sodium in Dogs After a Single Intravenous Administration at a Dose of 10 mg/kg BW." Study # 7926-2002-0095

1 Investigators: Brown, S.A., Modric, S., Pharmacia & Upjohn

2 Purpose: The purpose of this study was to obtain contemporary IV data for cefpodoxime sodium salt.

3 Type of Study: This was a single-treatment, single-dose study.

4 Treatment Groups: Twelve Beagle dogs (body weights ranging from 8 to 16 kg) were administered cefpodoxime sodium (PNU-76253A) intravenously as a single IV dose of 10 mg cefpodoxime equivalents/kg body weight.

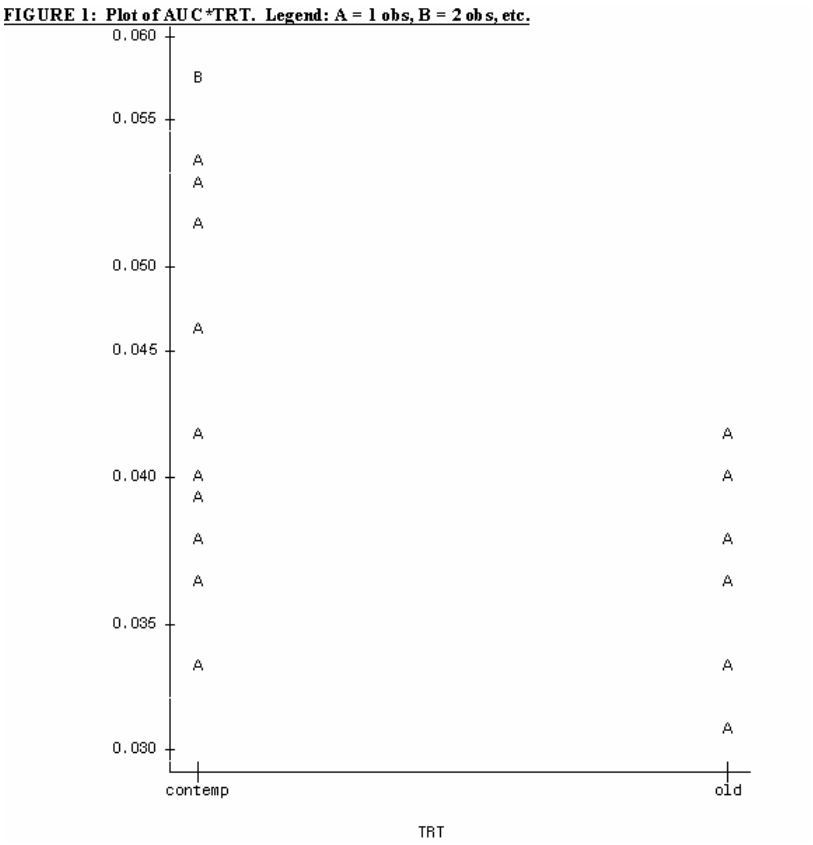
5 Measurements and Observations: Blood samples were collected prior to drug administration, and at 0.5, 1, 1.5, 2, 2.5, 3, 5, 8, 12, 16, 24, 36, and 48 hours after drug administration. Plasma was separated and stored until analysis by HPLC-UV.

6 Results: The average values for the terminal elimination half-life was 4.67 (± 0.680) hr, and the average $AUC_{0\text{-}\infty}$ was 454 (± 83.1) hr•mcg/mL. The values (mean, %CV) for VDss, VD_{λ} and CL_{total} = 0.134 (15) L/kg, 0.151 (18) L/kg, and 0.023 L/hr/kg (18), respectively. These values are similar to those estimated on the basis of the Rover IV dataset.

(4) TAS Bridging: Cross Study Data Analysis:

Both the estimate of the basic pharmacokinetic parameters (VD_{ss} and CL_{total}) and the individual subject AUC values associated with the two datasets show a high degree of overlap (Figure 1). Therefore, pooling of the Royer and Brown IV

datasets was considered appropriate for estimating the IV $AUC_{0\text{-}inf}$ values that will be used when calculating the margin of safety obtained in studies employing the bulk drug.



Using the pooled IV $AUC_{0\text{-}inf}$ data (normalized to a 1 mg/kg dose to facilitate comparisons), the margin of safety for the tablet and suspension are as follow:

$AUC_{0\text{-}inf}$ bulk drug/$AUC_{0\text{-}inf}$ mean IV: 12.67 mcg*hr/mL/41.1 mcg*hr/mL = **0.308**
$AUC_{0\text{-}inf}$ suspension/$AUC_{0\text{-}inf}$ mean IV = F suspension* 1.11 =
1.11 *(16.4 mcg*hr/mL/41.1 mcg*hr/mL) = **0.44**
$AUC_{0\text{-}inf}$ tablet/$AUC_{0\text{-}inf}$ mean IV = F tablet* 1.33 =
1.33*(16.1 mcg*hr/mL/41.1 mcg*hr/mL) = **0.52**

Based upon the safety demonstrated with the administration of a 100 mg/kg dose of the bulk drug in capsule, we conclude that the intended marketed formulation of the suspension and tablet will have the following margins of safety:

Margin of safety **suspension** = Safety study margin * corrected F bulk drug/ F suspension = (100 mg/kg/10 mg/kg)* (0.308/0.44) = **7.0**

Margin of safety **tablet** = Safety study margin * corrected F bulk drug/F tablet = (100 mg/kg/10 mg/kg)* (0.308/0.52) = **5.9**

4. HUMAN SAFETY:

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

Human Warnings are provided on the product label as follows: "Not for human use. Keep this and all drugs out of the reach of children. Antimicrobial drugs, including penicillins and cephalosporins, can cause allergic reactions in sensitized individuals. To minimize the possibility of allergic reactions, those handling such antimicrobials, including cefpodoxime, are advised to avoid direct contact of the product with the skin and mucous membranes."

5. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that SIMPLICEF tablets, when administered under the labeled conditions of use, are safe and effective for the treatment of skin infections (wounds and abscesses) in dogs caused by susceptible strains of *Staphylococcus intermedius, Staphylococcus aureus, Streptococcus canis* (group G, β hemolytic), *Escherichia coli, Pasteurella multocida,* and *Proteus mirabilis.*

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is needed in the diagnosis of bacterial infections in dogs, treatment of these conditions, and monitoring for possible adverse effects of the drug.

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

6. ATTACHMENTS:

Facsimile labeling is attached as indicated below:
Package Insert
Bottle label - 100 mg

Bottle label – 200 mg