Date of Approval: April 25, 2008

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-285

CONVENIA

Cefovecin sodium
Injectable
Cats and Dogs

For the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of *Pasteurella multocida.*

For the treatment of skin infections (secondary superficial pyoderma, abscesses, and wounds) in dogs caused by susceptible strains of *Staphylococcus intermedius* and *Streptococcus canis* (Group G).

Sponsored by:

Pfizer, Inc.

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I. GENERAL INFORMATION: CATS

A. File Number:	NADA 141-285
B. Sponsor:	Pfizer, Inc. 235 East 42d St. New York, NY 10017 Drug Labeler Code: 000069
C. Proprietary Name(s):	CONVENIA
D. Established Name(s):	Cefovecin sodium
E. Pharmacological Category:	Antimicrobial
F. Dosage Form(s):	Injectable
G. Amount of Active Ingredient(s):	Each mL of reconstituted sterile injectable lyophile contains 80 mg of cefovecin as the sodium salt.
H. How Supplied:	CONVENIA is supplied as a multi-use vial equal to 80 mg/mL when reconstituted with 10 mL sterile water for injection.
I. How Dispensed:	Rx
J. Dosage(s):	CONVENIA should be administered as a single, one-time subcutaneous injection at a dose of 3.6 mg/lb (8 mg/kg) body weight. After an injection of CONVENIA, therapeutic concentrations are maintained for approximately 7 days for *Pasteurella multocida* infections.
K. Route(s) of Administration:	Subcutaneous injection
L. Species/Class(es):	cats
M. Indication(s):	For the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of *Pasteurella multocida*.

II. EFFECTIVENESS:

A. Dosage Characterization:

The minimum inhibitory concentrations (MICs) were determined for 45 clinical *Pasteurella multocida* isolates from infections in cats using applicable Clinical and Laboratory Standards Institute (CLSI) standards. The MIC value inhibiting 90% of isolates (MIC_{90}) was calculated. The MIC_{90} for *P. multocida* was ≤ 0.06 µg/mL. This value was used for the pharmacokinetic analyses used to support the dosage characterization of CONVENIA.

1. Binding of Cefovecin to Cat Plasma Proteins: *In Vitro* Binding of Cefovecin (UK-287,074) to Cat Plasma Proteins

   This study (1680E-60-04-307) was conducted to determine the extent of *in vitro* binding of cefovecin to proteins in cat plasma. To estimate the relationship between free drug concentrations and the observed total cefovecin drug concentrations, the Hill function parameter values were estimated using SAS Proc NLIN. Using ln-transformed data for the estimated free and total drug concentrations, the fitted equation was:

   $$\% \text{ Free} = 0.241 + 99.759 \, Ctotal^{8.01} / (Ctotal^{8.01} + 195.1^{8.01})$$

   where $0.241 = C_0$ = the asymptotic binding of cefovecin (% free) as total cefovecin concentrations approach zero, C_{total} = the measured total cefovecin concentration, $99.759 = (100 - C_0)$; 195.1 is the total cefovecin concentration at which the percent free = $(100-C_0)/2$; and 8.01 is the shape factor.

   The percent protein binding in cat plasma was determined using equilibrium dialysis. The percent protein binding decreased in a nonlinear manner, ranging from 99.5% to 99.8% protein binding within the range of total plasma drug concentrations observed following a single 8 mg/kg injection to cats (10 – 100 µg/mL). Therefore, less than 0.5% of the total drug concentrations existed as free drug in the plasma. It is the free (unbound) drug that is available to exert antimicrobial effects.

2. Population Pharmacokinetics (PPK) of Cefovecin in Cats: Development of a Model and Simulation of Free Plasma Cefovecin Concentrations from the Intended Regimen

   Data used in the development of the PPK model came from four studies and are summarized in Table 1.

Table 1: Summary of Subject Demographics for the Four Studies

Study	No. Cats	Sex	Age Range (yr)	BW Range (kg)
1580P-60-99-220	6	3 M / 3 F	1.02 – 1.18	2.55 – 6.35
1580E-60-03-301	6	3 M / 3 F	1.0 – 1.25	4.13 – 7.31
5582N-36-99-197	6	3 M/ 3 F	0.6 – 1.38	2.9 – 4.4
5881W-36-04-237	4	2 M/ 2 F	1.1 – 8.1*	3.0 – 6.5
Pooled Data	22	11 F/ 11 M	Generally Young Adult	2.55-7.31

* Three of the four cats in this study ranged in age from 1.1 – 2.1 yrs.

The plasma cefovecin concentration data were pooled from these studies based upon the following criteria:

- Treatment with a single subcutaneous (SC) dose of cefovecin at 6.7 – 9.8 mg/kg body weight
- Individually housed cats
- Serial blood sampling beginning no later than 4 hours after dosing and continuing for at least 21 days (at least 12 post-dose PK blood samples/cat).
- LC/MS/MS analytical methodology to determine total plasma cefovecin concentrations.

One of the above studies (Study 5582N-36-99-197) evaluated the PK of CONVENIA following IV and SC single-dose administration at 8 mg/kg, and determined the absolute bioavailability of CONVENIA following the SC dose. Table 2 shows the individual study values for the first period of SC administration.

Table 2: Feline Pharmacokinetic Parameters Reflecting Total Drug Concentrations in Plasma (Mean ± Standard Deviation) Following Intravenous and Subcutaneous Administration of 8 mg/kg of Cefovecin in Cats

Parameter	Mean ± SD[1]
Terminal plasma elimination T (h)*[H]	166 (147, 190)
$AUC_{0\text{-inf}}$ (µg·h/mL)*[G]	22700 ± 3450
Time to maximum concentration, T_{max} (h)*[H]	2.0 ± 2.0
Maximum concentration, C_{max} (µg/mL)*[A]	141 ± 11.8
Vdss (L/kg)**[G]	0.090 ± 0.010
CL_{total} (mL/h/kg)**[G]	0.350 ± 0.40

[1] SD = standard deviation
* = Data from 6 subjects receiving a single subcutaneous dose of 8 mg/kg cefovecin
** = Data from 6 subjects receiving a single intravenous dose of 8 mg/kg cefovecin
A = arithmetic mean
H = harmonic mean (minimum estimated value, maximum estimated value)
G = geometric mean

The pooled plasma cefovecin concentration data from the above four studies resulted in a PPK dataset with 338 concentration records from 22 cats. Three of the four studies used an internal standard, cephalexin, which was added to the plasma samples before extraction. Study 1580P-60-99-220 did not use the internal standard. The precision and accuracy of the plasma analysis was shown to be similar across all four investigations.

Details regarding the PPK analysis are provided in the canine portion of this FOI summary. The model parameters generated in study 1680E-60-04-307 were used to estimate the percentage of free cefovecin through the range of anticipated total cefovecin plasma concentrations. Table 3 provides the PPK parameter values.

Table 3: Parameter Values from the Cat PPK Model

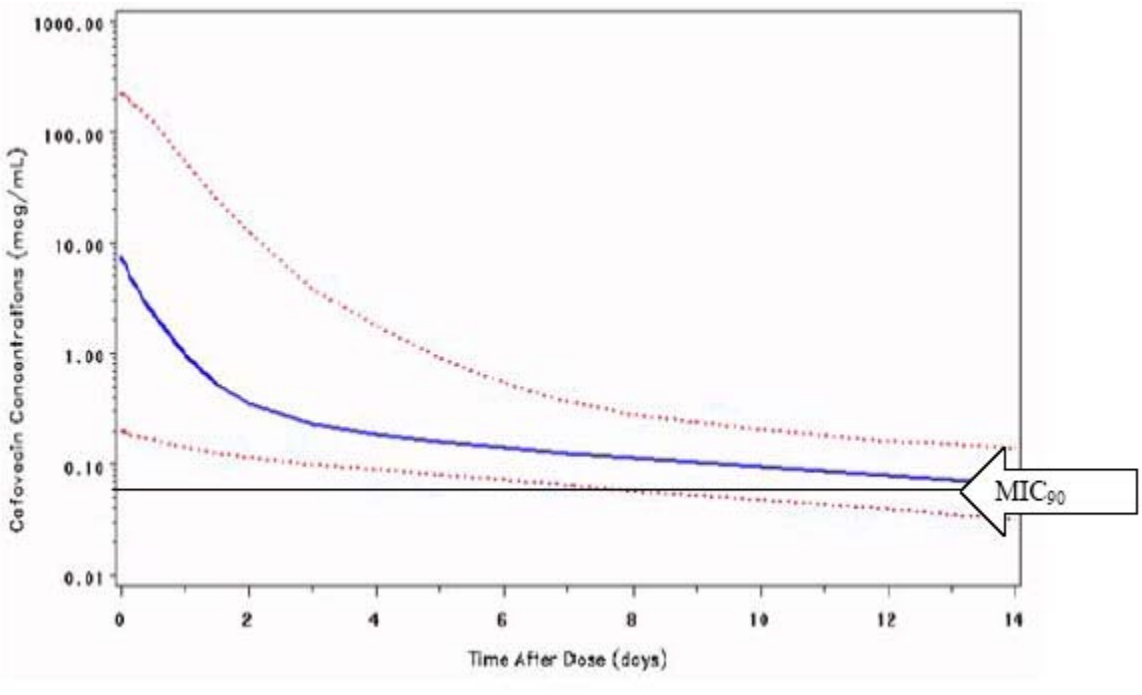
Parameter	Population Value (%SE)	95% Range of Values	Inter-Individual SD (% SE)*
CL/F (mL/h/kg)	0.293 (8.0)	0.256-0.334	0.342 (25.8)
Vp/F (mL/kg)	58.3 (7.2)	50.3-67.1	0.344 (24.8)
Vt/F (mL/kg)*	17.7 (10.5)	14.6-20.7	ND
Q/F (mL/h/kg)*	0.443 (38.8)	0.264-0.775	ND
SD of Residual Error	0.166 (8.1)	0.153-0.179	ND

* 95% range of values for Inter-Individual SD in CL/F and Vp/F = 0.232 – 0.427 and 0.226 – 0.430, respectively. Correlation between CL/F and Vp/F and 95% range of values = 0.919 and 0.823 – 0.974, respectively.

The individual parameter values generated during the successful parametric bootstrap simulations (498 data sets with 10,956 cats) were used to simulate (total) plasma cefovecin concentrations from a single 8 mg/kg SC dose. Free (unbound) cefovecin concentrations were estimated from the simulated total plasma cefovecin concentrations, based on the fit of a Hill function, to plasma protein binding data. Plasma protein binding data measured in an *in vitro* system using equilibrium dialysis were employed. SAS Proc NLIN was used to estimate the Hill function parameter values, and a SAS program was then used to estimate the time interval that the predicted free cefovecin concentrations remained above the minimum inhibitory concentration of the feline skin pathogen, *P. multocida*, which is associated with an MIC_{90} value of 0.06 µg/mL.

Figure 1 shows the modeled results of mean total and free concentration of cefovecin in plasma following a single subcutaneous injection of 8 mg/kg body weight in cats. The simulations indicated that > 95% of cats will have free plasma cefovecin concentrations ≥ 0.06 µg/mL for 7 days after an 8 mg/kg SC dose.

Figure 1: Predicted Free Concentrations of Cefovecin in Plasma Following a Single Subcutaneous Injection of 8 mg/kg Body Weight in Cats (Population Prediction and 90% Confidence Interval)



Conclusions: The PPK model, together with the MIC_{90} of the target pathogen, confirms that 95% of the potential feline patient population will have active (unbound) cefovecin plasma concentrations exceeding the MIC_{90} of the targeted pathogen (0.06 µg/mL) for approximately 7 days. This conclusion supports a dosage of 8 mg/kg body weight administered subcutaneously in cats, for the treatment of skin infections (wounds and abscesses) caused by the target pathogen (*P. multocida*).

3. Radiolabeled Cefovecin Study in Cats: Excretion of Radiolabel Following a Single Subcutaneous Dose of [14C]Cefovecin at 8 mg/kg to Cats.

   This study was conducted to determine the urinary and fecal excretion of radiolabel following a single subcutaneous dose of [14C]Cefovecin to cats and to estimate the total cefovecin residence time in the cat.

   Four male and four female cats received an 8 mg/kg dosage at a volume of 0.1 mL/kg. Following the radiolabeled dose, urine, feces, and plasma samples were collected.

   Based upon a ln-linear regression of the terminal portion of the concentration-time profile for the radio-labeled compound, the terminal elimination rate constant for cefovecin was observed to be 13 days in some cats.

   The results of the radiolabeled cefovecin study in cats indicate the potential persistence of cefovecin in the body. Based on the half life (T½ of 13 days) estimates provided in the radiolabel study, approximately 65 days is needed to eliminate 97% of the administered dose from the body.

B. Substantial Evidence:

The effectiveness of CONVENIA in the treatment of naturally occurring skin infections (wounds and abscesses) in cats presented as veterinary patients was evaluated in a controlled, masked study. CONVENIA was administered subcutaneously at the recommended dosage of 8 mg/kg in the commercial formulation. Twenty-six veterinary practices located in 13 States within the United States enrolled cats in this study.

1. Study Title: Efficacy and Safety of Cefovecin in the Treatment of Skin Infections in Cats Presented as Veterinary Patients

2. Type of Study: Multi-center, effectiveness study (GCP) involving 291 cats.

3. Investigators:

Susan Baker, DVM West Palm Beach, FL	Mildred Bass, DVM Farragut, TN
JoAnna Bender, DVM Rochester, NY	Brett Berryhill, DVM Baton Rouge, LA
Michael Bomar, DVM Wichita Falls, TX	Gary Brotze, DVM New Braunfels, TX
Bruce Coston, DVM Woodstock, VA	Bill Craig, DVM San Antonio, TX
Peter Davis, DVM Augusta, ME	Mark Girone, DVM Antioch, TN
William Greene, DVM Russ Anderson, DVM Nashville, TN	Larry Hendricks, DVM Germantown, TN
Theresa Hendrickson, DVM Manassas, VA	Stephen L. Jones, DVM Moncks Corner, SC
Charles Koenig, VMD Limerick, PA	Sharon Lachette, VMD White Haven, PA
William Lambert, DVM Milan, TN	John McCormick, DVM Nashville, TN
Ken McMillan, DVM Cropwell, AL	Susan Moon, DVM Memphis, TN
Dean Rund, DVM Springfield, MO	Roger Sifferman, DVM Springfield, MO
Brad Theodoroff, DVM Rochester Hills, MI	Gregory Tremoglie, VMD Glenmoore, PA
Carol Wolff, DVM Falmouth, ME	Philip Waguespack, DVM Baton Rouge, LA

4. General Design:

a. Purpose of Study: To confirm the effectiveness of CONVENIA against naturally occurring skin infections (wounds and abscesses) in cats when administered once, subcutaneously at 3.6 mg/lb (8 mg/kg) body weight.

b. Description of Test Animals: Two hundred and ninety-one (291) cats were randomly assigned to a single subcutaneous injection of 8 mg/kg CONVENIA (147 cats aged 2.4 months to 21 years) or 10 mg/lb cefadroxil administered orally once daily for 14 days. Four different pure and 5 different mixed breeds of cats were treated with CONVENIA.

c. Control and Treatment Group(s):

Table 4: Treatment Groups

Tx Group	Dose mg/kg	Number of cats enrolled (# evaluable)
cefovecin	3.6 mg/lb (8 mg/kg)	147 (89)
cefadroxil	10 mg/lb once daily orally	144 (88)

d. Inclusion Criteria: Cats enrolled in the study had a clinically significant skin infection characterized by a "moderate or severe" scoring of one or more of the following clinical signs at the time of enrollment: nodules, furuncles, erythema, purulent discharge and/or swelling. In addition, the presence of pathogenic bacteria was confirmed by microbiological culture via a sample collected from the infection site prior to treatment.

e. Exclusion Criteria: Cats not having a positive pre-treatment bacterial culture and cats not scoring at least one moderate/severe rating in the clinical categories were excluded from the study.

f. Dosage Form:

CONVENIA - Final market formulation CONVENIA was reconstituted with sterile water for injection prior to administration (80 mg/mL of cefovecin).

Cefadroxil - oral suspension 50 mg/mL

g. Route of Administration:

CONVENIA - subcutaneous injection
Cefadroxil - oral administration

To facilitate masking, cats allocated to the CONVENIA group also received an oral placebo and cats allocated to the cefadroxil group also received a placebo injection. Therefore, none of the individuals involved in the study (including but not limited to those individuals performing effectiveness assessments) were aware of the treatment groups.

h. Study Duration: 28 days

i. Variables Measured:

Effectiveness was assessed based on clinical signs of skin infection. Clinical signs were scored by the Examining Veterinarian as being absent, mild,

moderate, or severe on Days 0 (prior to treatment), 7, 14, and 28. At the time of the final assessment, the Examining Veterinarian also provided an evaluation of the overall clinical outcome of each case.

Baseline clinical pathology values (hematology, clinical chemistry, and urinalysis) were collected prior to treatment administration and at study end. Abnormal health observations and concurrent medications administered to each cat were recorded. In addition, any injection site abnormalities were recorded for each animal.

Microbiological cultures were obtained from each cat at the beginning of the study, and from any cat with a lesion (treatment failures) to culture at the end of the study.

j. Statistical Analysis:

A cat successfully completed the study if each clinical sign initially classified as moderate or severe was reduced to mild or absent by Day 28. The percentage of cats successfully treated was calculated at Day 14 and Day 28. Cats withdrawn from the study due to lack of effectiveness were considered treatment failures.

The determination of effectiveness was based on the number of cats successfully completing the study 28 days after initiation of treatment.

A per protocol population was defined for effectiveness analysis. The per protocol population consisted of cats that were randomized to treatment and met all of the inclusion criteria, none of the exclusion criteria, received at least one dose of either CONVENIA or cefadroxil and had sufficient observations for effectiveness evaluation.

A non-inferiority test was conducted for the percent of cases successfully treated in the two treatment groups and completing the study. Non-inferiority was concluded if the one-sided lower limit of the difference between percentages of successful completion was above the non-inferiority margin. This test was conducted on the per protocol population animals at a one-sided 5% significance level and a non-inferiority margin of 15 percentage points. A secondary non-inferiority analysis was conducted excluding those that missed three or more doses of cefadroxil.

5. Results:

There were 291 cats enrolled in the study. This included 147 CONVENIA cases and 144 cefadroxil cases. One hundred and fourteen cases (114) were excluded from the effectiveness evaluation. The most common reason for exclusion was failure to confirm a viable isolate during bacterial identification

and minimum inhibitory concentration testing. Other reasons for exclusion were failure to meet inclusion criteria, insufficient number of evaluable cases from a site, missing or incomplete microbiology data, and extreme scheduling deviations for the final assessment visit.

The effectiveness evaluation was based on 89 CONVENIA cases and 88 cefadroxil cases. This included eight cats that withdrew from the study prior to completion due to lack of effectiveness or adverse reactions. These cats were considered treatment failures.

The percentage of cats from evaluable cases (CONVENIA- and cefadroxil-treated) with clinical signs of skin infection (purulent discharge, swelling, erythema, nodules, and furuncles) is summarized in Table 5.

Table 5: Percentage of Cats with Clinical Signs of Skin Infections (Wounds and Abscesses)

Clinical Sign	Treatment	Day 0	Day 7	Day 14	Final Assessment (Day 28)
Purulent Discharge	CONVENIA	95.5	12.4	1.2	0.0
	cefadroxil	96.6	15.3	3.6	6.1
Swelling	CONVENIA	98.9	34.8	10.6	0.0
	cefadroxil	93.2	40.0	9.5	6.1
Erythema	CONVENIA	89.9	44.9	11.8	0.0
	cefadroxil	93.2	38.8	15.5	4.9
Nodules	CONVENIA	0.0	0.0	0.0	0.0
	cefadroxil	8.0	4.7	2.4	0.0
Furuncles	CONVENIA	2.2	0.0	0.0	0.0
	cefadroxil	4.5	3.5	1.2	1.2

Notes:
1. Includes all evaluable animals in the per protocol population
2. Actual study observation days for Day 0: -3 to 0, Day 7: 5 to 9, Day 14: 16 to 19, Day 28: 25 to 38.
3. Number of CONVENIA animals observed on Day 0: 89; Day 7: 89 Day 14: 85, Day 28: 81
   Number of cefadroxil animals observed on Day 0: 88; Day 7: 85 Day 14: 84, Day 28: 82
4. By Day 28 assessment, some cats were lost due to treatment failures, adverse reactions, and no final assessment.

Fourteen days after injectable treatment administration (Day 14), each clinical sign of skin infection had been reduced to mild or absent in 87/89 (97.8%) of CONVENIA-treated cats and in 84/88 (95.5%) of cefadroxil-treated cats.

Twenty-eight days after injectable treatment administration (Day 28), each clinical sign of skin infection had been reduced to mild or absent in 86/89 (96.6%) of CONVENIA-treated cats and in 80/88 (90.9%) of cefadroxil-treated cats.

Using a non-inferiority margin of 15%, CONVENIA was determined to be non-inferior to cefadroxil 28 days after injectable treatment (Table 6).

Based on the Examining Veterinarian's assessment of the overall clinical outcome of each case 28 days after injectable treatment, 85 (95.5%), 2 (2.2%), and 2 (2.2%) of the CONVENIA-treated cats and 77 (87.5%), 3 (3.4%) and 8 (9.0%) of the cefadroxil-treated cats were cured, improved or failed, respectively. One CONVENIA case was considered a treatment failure due to an adverse reaction, not lack of effectiveness. This cat was assessed by the veterinarian as a success based on clinical outcome. Refer to Table 6.

Table 6: Number and Percentage of Cats Successfully Treated During the Study

	Number (Percentage) of Cats Successfully Completing Study[1]			
	Day 14 Assessment		**Day 28 Assessment (Final)**	
Treatment	Yes	No	Yes	No
CONVENIA	87 (97.8%)	2 (2.2%)	86 (96.6%)[2]	3 (3.4%)
cefadroxil	84 (95.5%)	4 (4.5%)	80 (90.9%)[2]	8 (9.1%)

[1]Successful completion defined as reduction in the severity of the clinical signs of skin infection (purulent discharge, swelling, erythema, nodules, and furuncles) to mild or absent in severity.
[2]CONVENIA non-inferior to cefadroxil ($\delta = 0.15$).

a. Concomitant Treatments

A variety of concomitant medications were administered to cats concurrently with cefovecin. These included heartworm preventatives, flea control products, sedatives/tranquilizers, anesthetic agents, and routine vaccinations.

b. Adverse Reactions:

Vomiting and diarrhea were the most common abnormal observations in both treatment groups. One CONVENIA cat was euthanized for testing positive for feline immunodeficiency virus.

A total of 291 cats were included in the field study safety analysis. Abnormal health observations reported in cats treated with CONVENIA and cefadroxil are summarized in Table 7.

Table 7: Number of Cats* with Adverse Reactions Reported During Field Study with CONVENIA		
Adverse Reaction	CONVENIA (n = 147)	cefadroxil (n = 144)
Vomiting	10	14
Diarrhea	7	26
Anorexia/Decreased Appetite	6	6
Lethargy	6	6
Hyper/Acting Strange	1	1
Inappropriate Urination	1	0

*Some cats may have experienced more than one adverse reaction or more than one occurrence of the same adverse reaction during the study.

c. Injection Site Observations:

CONVENIA or injectable placebo was administered by the Examining Veterinarian subcutaneously at a site free of any pre-existing abnormalities and not near the sites of other injectable treatments. Injections were administered in five anatomical regions: thorax, forelimb, hind limb, dorsal scapula or lumbar region. The percentage of cefovecin-treated cats receiving treatment at each site are as follows: thorax 39%, left and right forelimb 23%, left and right hind limb 18%, dorsal scapula 11%, and lumbar 10%.

There were no abnormal injection site observations in CONVENIA-treated cats.

d. Clinical Pathology:

There were no notable differences between mean values for all laboratory tests among CONVENIA and cefadroxil-treated cats. For individual laboratory values, the following findings are noted:

There were 16 CONVENIA cases with decreased WBC counts post-study (< 5.5 X $10^{-3}/mm^3$).

There were four CONVENIA cases with normal hematocrit values pre-study and decreased hematocrit values post-study. Another CONVENIA case had a pre-study hematocrit of 19.2% and a post-study hematocrit of 10.5%. This cat was 4.2 lbs and 8 months old. There is no follow up on this cat after Day 28.

Many CONVENIA cases had decreased pre-study and post-study platelet values. This is not an uncommon finding in cats due to the tendency for platelet clumping.

Four CONVENIA cases had elevated post-study ALT (alanine aminotransferase) levels (normal range = 0 – 120 IU/L). One case was elevated pre-study.

There were 24 CONVENIA cases with normal pre-study BUN (blood urea nitrogen, normal range = 10 - 30 mg/dL) values and elevated post-study BUN values (ranging from 37 – 39 mg/dL post-study).

There were six CONVENIA cases with normal pre- and elevated post-study creatinine values (normal range = 0.8 – 2.0 mg/dL). Two of these cases also had an elevated post-study BUN.

There were 10 CONVENIA cases with elevated post-study calcium levels (normal range 8.8 – 11.0 mg/dL). It is noted that the post-study albumin levels were high for seven of these cases.

None of the animals showed clinical signs associated with these laboratory changes.

e. Microbiology:

CONVENIA is a cephalosporin antibiotic. Like other β-lactam antimicrobials, CONVENIA exerts its inhibitory effect by interfering with bacterial cell wall synthesis. This interference is primarily due to its covalently binding to the penicillin-binding proteins (PBPs) (i.e., transpeptidase and carboxypeptidase), which are essential for synthesis of the bacterial cell wall.

Identification of bacterial pathogens was made to the species level, based on morphology, Gram stain, growth characteristics, standard individual biochemical testing and/or commercially available identification test kits. Minimum inhibitory concentration (MIC) testing was conducted in accordance with applicable Clinical and Laboratory Standards Institute (CLSI) standards. CONVENIA MICs for the pre-treatment bacterial pathogens isolated from enrolled cats are summarized in Table 8.

Table 8: Activity of CONVENIA Against Pathogens Isolated from Cats Treated With CONVENIA in Field Studies in the U.S. During 2001-2003

Disease	Pathogen	Microbiological Treatment Outcome	Number of Isolates	Sample Collection (Time Relative to Treatment)	MIC_{50} µg/mL	MIC_{90} µg/mL	MIC Range µg/mL
Skin infections	*Pasteurella multocida*	Success	57	Pre-Treatment	≤ 0.06	≤ 0.06	≤ 0.06 - 0.12
		Failure	1	Pre-Treatment			≤ 0.06

6. Conclusions:

CONVENIA administered as a single subcutaneous injection at a dose of 3.6 mg/lb (8 mg/kg) body weight was effective against naturally occurring skin infections (wounds and abscesses) in cats against susceptible strains of *Pasteurella multocida*.

III. TARGET ANIMAL SAFETY:

A. Drug Tolerance Study:

1. Type of Study: Laboratory safety study (GLP)

2. Study Director: Michael C. Savides, PhD.
Ricerca, LLC
Concord, OH

3. General Design:

a. Purpose: To determine the toxic effects of CONVENIA when administered once subcutaneously to cats at an exaggerated dose (180 mg/kg body weight).

b. Test Animals: Twelve healthy cats (6M and 6F), approximately 7 months of age, were randomly assigned to either CONVENIA or the control group (three/sex/group).

c. Control: Injectable Sodium Chloride (0.9% sterile)

d. Dosage form: Final market formulation, 80 mg/mL of CONVENIA

e. Route of administration: Dorsoscapular subcutaneous injection

f. Dosages used:

Treatment Groups for the Drug Tolerance Study

Group	Dose mg/kg	Number and Sex of Cats
1	0 mg/kg (saline)	3 males, 3 females
2	180 mg/kg	3 males, 3 females

g. Test duration: Thirty days

h. Variables measured: Clinical observations, physical exams, injection site evaluations, body weight, hematology, serum chemistry, coagulation tests, plasma drug concentrations, urinalysis, and food consumption were assessed.

4. Results: All cats survived to termination of the study.

a. Abnormal clinical findings included vocalization and scratching. Edema associated with the CONVENIA injection sites occurred within two hours of the administration. All edema resolved within eight hours of the CONVENIA injection.

b. Hematology and serum chemistry: The mean WBC counts were lower in the cefovecin group (mean WBC = 10.93) than in the control group (mean WBC = 14.48) at Day 10. All mean WBC counts remained within the normal range[1] [5.5-19.5 X $10^3/mm^3$ for the study lab].

c. Urinalysis: One cat in the CONVENIA group had a small amount of bilirubinuria on Day 10.

d. Plasma drug concentrations: In both the male and female cats, concentrations of CONVENIA were greatest at the initial sampling time (1.5 hours), and remained above the limit of detection (0.05 mcg/mL) for the duration of the study. These data indicate that cefovecin was rapidly absorbed and has a prolonged time for elimination from the plasma.

5. Conclusions: Under the conditions of this study, the cats remained healthy throughout the 30-day study duration. Irritation immediately following injection and transient injection site edema occurred within two hours of administration. All edema resolved within eight hours.

[1] Duncan, J.R., Prasse, K.W., and Mahaffey, E.A. 1994. Veterinary Laboratory Medicine, Third Edition. Iowa State University Press, Ames.

B. Margin of Safety and Injection Site Tolerance of Cefovecin Injectable Solution in Cats:

1. Type of Study: Laboratory safety study (GLP)

2. Study Director: Elizabeth Evans, DVM
Midwest Research Institute (MRI)
Kansas City, MO

3. General Design:

a. Purpose: To evaluate the safety and injection site toleration of CONVENIA when administered subcutaneously, once every 7 days for a total of five injections in cats.

b. Test Animals: Thirty-two healthy cats (16M and 16F), approximately 12-16 weeks of age, were randomly assigned to the four dose groups.

c. Control: Injectable Sodium Chloride (0.9% sterile)

d. Dosage form: Final market formulation, 80 mg/mL of CONVENIA

e. Route of administration: Dorsoscapular subcutaneous injection

f. Dosages used:

Treatment Groups for Safety Study

1) Control (saline) every seven days for four consecutive weeks (5 total doses)
2) 12 mg/kg (1.5 X) every seven days for four consecutive weeks (5 total doses)
3) 36 mg/kg (4.5 X) every seven days for four consecutive weeks (5 total doses)
4) 60 mg/kg (7.5 X) every seven days for four consecutive weeks (5 total doses)

g. Test duration: Forty-two days

h. Variables measured: Evaluations included clinical signs, general health observations, physical examinations, body weight, hematology, coagulation tests, serum chemistry, urinalysis, fecal examination, gross pathology and histopathology, injection site evaluations, and plasma blood concentrations.

4. Results: All cats survived to termination of the study.

a. Clinical observations: Soft, thickened palpable lesions (1/2 cm or less)

were associated with the injection sites of the control and CONVENIA-treated cats. Most injection site swellings occurred within one hour of administration. The largest (width X length) swelling noted for the injection sites was 3 mm X 3 mm. This was seen in one cat in the 36 mg/kg group and two cats in the 60 mg/kg group. The occurrence of injection site swellings increased with the number of injections given. Irritation and vocalization occurred in some cats following administration of high doses. There were a statistically significant greater number of cats ($p < 0.1$) in the 60 mg/kg group compared to the controls with injection site swellings after the 3rd and 4th injections. See Table 9 below. All swellings resolved within 12 hours of drug administration.

Table 9: Number of Cats/Group with Injection Site Swelling

	Control	12 mg/kg	36 mg/kg	60 mg/kg
1st injection	0	0	1	2
2nd injection	0	1	3	1
3rd injection	0	1	2	4*
4th injection	3	3	7	8*
5th injection	3	4	5	7

* $p < 0.1$, statistically significant

Lip lesions consistent with eosinophilic granulomas were seen in all four study groups throughout the study. Incidences of vomiting and diarrhea increased with increasing dose. Diarrhea often lasted three or more days following injections in the 60 mg/kg group.

b. Hematology and serum chemistry: There was a trend toward decreasing mean neutrophil percentage values seen with increasing dose.

The mean albumin levels for the CONVENIA groups were significantly lower than the control group for all in-study time points ($p < 0.01$ for time points 1, 2, 3, and 4; and $p < 0.05$ at time point 5). All means remained within the normal reference range for this lab [normal range = 2.5 - 3.9 gm/dL]. See Table 10.

Table 10: Mean Albumin Values at In-Study Time Points

	Mean albumin value (gm/L)			
Time Point	Control group	12 mg/kg group	36 mg/kg group	60 mg/kg group
Day 6 - 7	3.450	3.112	2.95	2.95
Day 12 - 13	3.475	3.213	3.113	3.075
Day 19 - 21	3.488	3.038	3.038	3.025
Day 26 - 28	3.600	3.238	3.150	3.050
Day 40 - 41	3.613	3.413	3.40	3.425

The mean alkaline phosphatase values were significantly higher ($p = 0.0291$) for the 60 mg/kg group compared to the control group over all time points [normal alkaline phosphatase range for this lab = 0 - 90 IU/L]. See Table 11.

Table 11: Mean Alkaline Phosphatase Values at In-Study Time Points

	Mean alkaline phosphatase value (IU/L)	
Time Point	Control group	60 mg/kg group
Day -8-1	93.75	118.125
Day 6-7	96.75	128.125
Day 12-13	90.75	117.125
Day 19-21	89.75	132.375
Day 26-28	91.125	138.250
Day 40-41	86.375	124.625

c. Pathology: Two cats in the 60 mg/kg group had small serosal to mucosal lesions (2 mm) in the duodenum. These two cats also exhibited diarrhea. This lesion also occurred in one control cat (no clinical signs of diarrhea). One cat in the 12 mg/kg group had a fibrotic kidney lesion of the tubules and interstitium. Another cat in this 12 mg/kg group showed mild glomerulosclerosis in one kidney. The relationship to drug administration could not be determined.

Hepatic lesions included minimal liver vacuolation in a 12 mg/kg cat, moderate liver vacuolation in one 36 mg/kg group cat, and one cat in the 36 mg/kg group with minimal liver inflammation.

Histopathological changes noted at the injection sites were minimal and included perivascular inflammation and minimal granulomatous, parafollicular inflammation.

d. Plasma drug concentrations: A less than dose proportional change in total drug exposure was seen as doses increased from 12 mg/kg to 60 mg/kg in cats. Accordingly, total drug peak and trough concentrations of CONVENIA in plasma were similar in cats receiving subcutaneous doses of 12 mg/kg, 36 mg/kg, and 60 mg/kg of CONVENIA. Concentrations were generally similar between male and female cats.

5. Conclusions: CONVENIA administered once every seven days for four consecutive weeks, at doses up to 60 mg/kg body weight did not produce toxicity in healthy cats. The relationship between mild renal and hepatic lesions and CONVENIA administration is not clear. Irritation and vocalization occurred following high dose administration in some cats. Edema at the injection sites resolved within 12 hours. Increased incidences of vomiting and diarrhea were associated with 36 mg/kg and 60 mg/kg doses of CONVENIA.

IV. GENERAL INFORMATION: DOGS

A. File Number:	NADA 141-285
B. Sponsor:	Pfizer, Inc. 235 East 42d St. New York, NY 10017 Drug Labeler Code: 000069
C. Proprietary Name(s):	CONVENIA
D. Established Name(s):	Cefovecin sodium
E. Pharmacological Category:	Antimicrobial
F. Dosage Form(s):	Injectable
G. Amount of Active Ingredient(s):	Each mL of reconstituted sterile injectable lyophile contains 80 mg of cefovecin as the sodium salt.
H. How Supplied:	CONVENIA is supplied as a multi-use vial equal to 80 mg/mL when reconstituted with 10 mL sterile water for injection.
I. How Dispensed:	Rx
J. Dosage(s):	CONVENIA should be administered as a single subcutaneous injection of 3.6 mg/lb (8 mg/kg) body weight. A second subcutaneous injection of 3.6 mg/lb (8 mg/kg) may be administered if response to therapy is not complete. The decision for a second injection for any individual dog should take into consideration such factors as progress toward clinical resolution, the susceptibility of the causative organisms, and the integrity of the dog's host-defense mechanisms. Therapeutic drug concentrations after the first injection are maintained for 7 days for *S. intermedius* infections and for 14 days for *S. canis* (Group G) infections. Maximum treatment should not exceed 2 injections.

K. Route(s) of Administration: Subcutaneous injection

L. Species/Class(es): Canine

M. Indication(s): For the treatment of skin infections (secondary superficial pyoderma, abscesses, and wounds) in dogs caused by susceptible strains of *Staphylococcus intermedius* and *Streptococcus canis* (Group G).

V. EFFECTIVENESS:

A. Dosage Characterization:

The minimum inhibitory concentrations (MICs) were determined for 69 clinical bacterial isolates from infections in dogs using applicable Clinical and Laboratory Standards Institute (CLSI) standards. MIC values inhibiting 90% of *Staphylococcus intermedius* and *Streptococcus canis* isolates (MIC_{90}) were calculated. The MIC_{90} for *Staphylococcus intermedius* was 0.25 µg/mL and for *Streptococcus canis* was ≤ 0.06 µg/mL. These values were used for the pharmacokinetic analyses used to support the dosage characterization of CONVENIA in dogs.

1. Binding of Cefovecin to Dog Plasma Proteins: *In Vitro* Binding of Cefovecin (UK-287,074) to Dog Plasma Proteins

This study was conducted to determine the extent of *in vitro* binding of cefovecin to proteins in dog plasma. To estimate the relationship between free drug concentrations and the observed total cefovecin drug concentrations, the Hill function parameter values were estimated using SAS Proc NLIN. The resulting fitted equation was:

$$\% \text{ Free} = 1.39 + 98.61\ C_{total}^{4.39} / (C_{total}^{4.39} + 184^{4.39})$$

where $1.39 = C_0$ = the asymptotic binding of cefovecin (% free) as total cefovecin concentrations approach zero, C_{total} = the measured total cefovecin concentration, $98.61 = (100 - C_0)$; 184 is the total cefovecin concentration at which the percent free = $(100\text{-}C_0)/2$; and 4.39 is the shape factor.

The percent protein binding in dog plasma was determined using equilibrium dialysis. The percent protein binding decreased in a nonlinear manner, ranging from 96% to 98.7% protein binding within the range of total plasma drug concentrations observed following a single 8 mg/kg injection to dogs (10 – 100 µg/mL). By Day 2 post-dose, less than 2% of

the total drug concentrations existed as free drug in the plasma. It is the free (unbound) drug that is available to exert antimicrobial effects.

2. Population Pharmacokinetics (PPK) of Cefovecin in Dogs: Development of a Model and Simulations to Predict Free Plasma Cefovecin Concentrations from the Intended Therapeutic Regimens

Data used in the development of the PPK model came from seven studies and are summarized in Table 12.

Table 12: Summary of Subject Demographics for the Seven Studies

Study	No. Dogs	Sex	Age Range (mo)	BW Range (kg)
5562N-36-99-210	6	3F/3M	11.6 – 16.5	11.4 - 15.3
5561C-36-00-218	12	5F/7M	10.5 – 25.5	12.7 – 16.9
5560E-36-01-236	3	3F/0M	>10†	10.0 – 20.0†
1560P-60-99-368	4	2F/2M	18.6 – 20.2	9.7 – 12.1
1560E-60-00-466	4	2F/2M	8.9 – 9.3	9.1 – 13.5
1560N-60-01-500	4	2F/2M	19 - 19	5.5 – 10.2
1560E-60-03-657	6	3F/3M	Adults†	6.7 - 9.6
Pooled Data	39	20F/19M	Generally Young Adult	5.5 – 20.0

†Protocol specified inclusion/exclusion criteria

The plasma cefovecin concentration data were pooled from these studies. Other common features of the seven studies included:

- Commercial prototype formulation
- At least 10 serial blood samples/dog for determination of plasma cefovecin concentrations with sampling beginning no later than four hours after dosing and continuing for at least 504 hours.
- LC/MS/MS analytical methodology to determine total plasma cefovecin concentrations

One of the above studies (Study 5562N-36-99-210) evaluated the PK of CONVENIA following IV and SC single-dose administration at 8 mg/kg, and determined the absolute bioavailability of CONVENIA following the SC dose. Table 13 shows the individual study values for the first period of SC administration.

Table 13: Pharmacokinetic Parameters Reflecting Total Drug Concentrations in Plasma (mean ± standard deviation) Following Intravenous and Subcutaneous Administration of 8 mg/kg of Cefovecin in Dogs

Parameter	**Mean ± SD[1]**
Terminal plasma elimination T (h)*[H]	133 (96, 206)
$AUC_{0\text{-}inf}$ (µg·h/mL)*[G]	10400 ± 1900 [p]
Time to maximum concentration, T_{max} (h)*[H]	6.2 ± 3.0
Maximum concentration, C_{max} (µg/mL)*[A]	121 ± 51
Vdss (L/kg)**[G]	0.122 ± 0.011
CL_{total} (mL/h/kg)**[G]	0.76 ± .0.13 [p]

[1] SD = standard deviation
p = a phase effect was observed, only data for the first phase are provided (n=6); all other data provided are derived from 12 animals
* = SC
** = IV
A = arithmetic mean
H = harmonic mean (minimum estimated value, maximum estimated value)
G = geometric mean

The pooled plasma samples from the 7 studies (591 concentration records) were analyzed using a sensitive and specific HPLC method with tandem mass spectrometric detection (LC/MS/MS). Five of the seven studies used an internal standard, cephalexin, which was added to the plasma samples before extraction; two studies did not use an internal standard. The precision and accuracy of the plasma analysis was shown to be similar across all seven investigations.

The program NONMEM version 6 was used to fit various PPK models to the data and to perform simulations to evaluate the stability of the final model. A two-compartment linear population pharmacokinetic model with a proportionate error structure was found to adequately describe the data. Structural model parameters were the population values of the 1st order absorption rate constant (Ka), total body plasma clearance (CL/F), the apparent volumes of distribution of the central and peripheral compartments (Vp/F, Vt/F, respectively), and the inter-compartmental clearance (Q/F). Inter-individual variability was estimated for CL/F and Vp/F, but not for any other parameters. A parametric bootstrap method was used to demonstrate the stability of the model, the accuracy of the model parameter values, and to obtain approximate confidence ranges for the parameters. Parameter values from the final model are listed in Table 14.

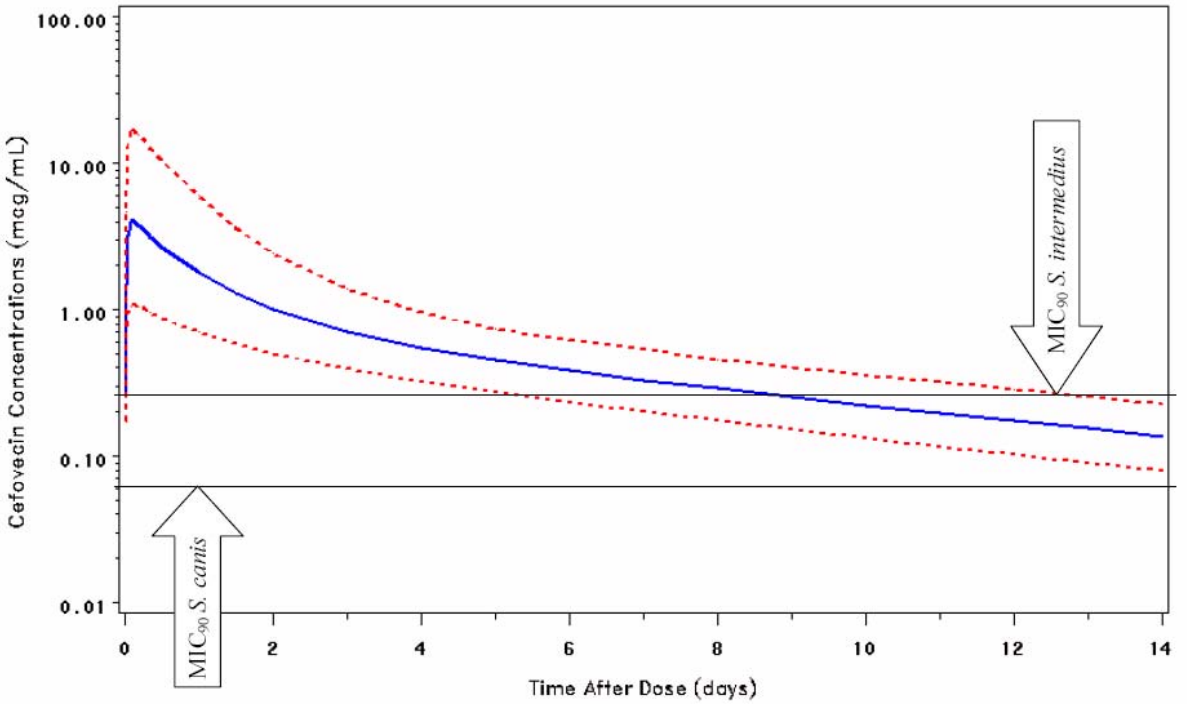
Table 14: Parameter Values for Final PPK Model

Parameter	Population Value (%SE)	95% Range of Values	Inter-Individual SD (% SE)
CL/F (mL/h/kg)	0.649 (2.7)	0.620 – 0.685	0.121 (33.9)
Vp/F (mL/kg)	90.2 (2.5)	86.0 – 95.7	0.145 (24.2)
Vt/F (mL/kg)*	27.9 (6.8)	24.1 – 31.4	ND
Q/F (mL/h/kg)*	0.410 (14.6)	0.294 – 0.557	ND
Ka (1/h)	2.56 (8.7)	2.20 – 3.01	ND
Correlation between CL/F and Vp/F	0.695 (ND)	0.451 – 0.881	ND
SD of Residual Error	0.192 (6.1)	17.8 – 20.4	ND

The individual parameter values generated during the successful parametric bootstrap simulations (499 data sets with >19000 dogs) were used to simulate (total) plasma cefovecin concentrations from two 8 mg/kg SC doses separated by either 7 or 14 days. Free (unbound) cefovecin concentrations were estimated from the simulated total plasma cefovecin concentrations, based on the fit of a Hill function to plasma protein binding data. Plasma protein binding data measured in an *in vitro* system using equilibrium dialysis were employed. SAS Proc NLIN was used to estimate the Hill function parameter values, and a SAS program was then used to estimate the time interval that the predicted free cefovecin concentrations remained above the minimum inhibitory concentration of the two indicated canine skin pathogens; MIC_{90} values of 0.25 µg/mL (*Staphylococcus intermedius*) or 0.06 µg/mL (*Streptococcus canis*) were used.

Figure 2 shows the modeled results of mean total and free concentration of cefovecin in plasma following a single subcutaneous injection of 8 mg/kg body weight in dogs. The simulations indicated that > 98% of dogs will have free plasma cefovecin concentrations ≥ 0.06 µg/mL for 14 days after an 8 mg/kg subcutaneous (SC) dose. Approximately 92% of dogs are predicted to have free plasma cefovecin concentrations ≥ 0.25 µg/mL for 6 days after an 8 mg/kg SC dose. Approximately 82 - 84% of dogs are predicted to have free plasma cefovecin concentrations ≥ 0.25 µg/mL at 7 days after the 8 mg/kg SC dose.

Figure 2. Predicted Free Concentration of Cefovecin in Plasma Following a Single Subcutaneous Injection of 8 mg/kg Body Weight in Dogs (Population Prediction and 90% Confidence Interval)



Conclusion: The PPK model, together with the MIC_{90} of the target pathogens, confirms that free cefovecin concentrations exceeded the MIC_{90} of *Staphylococcus intermedius* (0.25 µg/mL) for 7 days in approximately 82 - 84% of dogs and the MIC_{90} of *Streptococcus canis* (0.06 µg/mL) for 14 days in > 95% of dogs. Thus, therapeutic drug concentrations after the first injection are maintained for 7 days for *S. intermedius* infections and for 14 days for *S. canis* (Group G) infections.

B. Substantial Evidence:

The effectiveness of CONVENIA in the treatment of naturally occurring skin infections (superficial secondary pyoderma, abscesses, and infected wounds) in dogs presented as veterinary patients was evaluated in a well-controlled, masked field study. CONVENIA was administered subcutaneously at the recommended dose of 8 mg/kg in the commercial formulation. Twenty-six veterinary practices located in 13 States within the United States enrolled patients in this study.

1. Study Title: Efficacy and Safety of Cefovecin in the Treatment of Skin Infections in Dogs Presented as Veterinary Patients

2. Type of Study: Multi-center, effectiveness study (GCP) involving 320 dogs.

3. Investigators:

Susan Baker, DVM West Palm Beach, FL	Mildred Bass, DVM Farragut, TN
JoAnna Bender, DVM Rochester, NY	Brett Berryhill, DVM Baton Rouge, LA
Michael Bomar, DVM Wichita Falls, TX	Gary Brotze, DVM New Braunfels, TX
Bruce Coston, DVM Woodstock, VA	Bill Craig, DVM San Antonio, TX
Peter Davis, DVM Augusta, ME	Mark Girone, DVM Antioch, TN
William Greene, DVM Russ Anderson, DVM Nashville, TN	Larry Hendricks, DVM Germantown, TN
Theresa Hendrickson, DVM Manassas, VA	Stephen L. Jones, DVM Moncks Corner, SC
Charles Koenig, VMD Limerick, PA	Sharon Lachette, VMD White Haven, PA
William Lambert, DVM Milan, TN	John McCormick, DVM Nashville, TN
Ken McMillan, DVM Cropwell, AL	Susan Moon, DVM Memphis, TN
Dean Rund, DVM Springfield, MO	Ralph Schoemann, DVM Guilford, CT
Roger Sifferman, DVM Springfield, MO	Brad Theodoroff, DVM Rochester Hills, MI
Gregory Tremoglie, VMD Glenmoore, PA	Carol Wolff, DVM Falmouth, ME

4. General Design:

a. Purpose of Study: To confirm the effectiveness of CONVENIA against naturally occurring skin infections (superficial secondary pyoderma, abscesses, and infected wounds) in dogs when administered subcutaneously at 3.6 mg cefovecin/lb body weight (8 mg/kg) once, or twice, 14 days apart, for a total of two treatments.

b. Description of Test Animals: Three hundred and twenty (320) dogs were randomly assigned to a single subcutaneous injection of 3.6 mg/lb (8 mg/kg) CONVENIA (157 dogs - aged 8 weeks to 19 years) or 10 mg/lb (22 mg/kg) cefadroxil (163 dogs - aged 10 weeks to 15 years) administered orally twice daily for 14 days. At the discretion of the examining veterinarian, a second injection of CONVENIA or a second 14-day course of cefadroxil was initiated 14 days after the initial treatment. Fifty different pure and 24 different mixed breeds of dogs were treated with CONVENIA.

c. Control and Treatment Group(s):

Table 15: Treatment Groups

Treatment Group	Dose	Number of dogs enrolled (# evaluable)
CONVENIA	3.6 mg/lb (8 mg/kg)	157 (118)
cefadroxil	10 mg/lb (22 mg/kg) once daily orally	163 (117)

d. Inclusion Criteria: Dogs enrolled in the study had a clinically significant skin infection characterized by a "moderate or severe" scoring of one or more of the following clinical signs at the time of enrollment: papules, pustules, nodules, furuncles, erythema, erosion/ulceration, purulent discharge, and/or swelling. In addition, the presence of pathogenic bacteria was confirmed by microbiological culture via a sample collected from the infection site prior to treatment.

e. Exclusion Criteria: Dogs not having a positive pre-treatment bacterial culture and dogs not scoring at least one moderate/severe rating in the clinical categories were excluded from the study.

f. Dosage Form:

CONVENIA - Final market formulation cefovecin was reconstituted with sterile water for injection prior to administration (80 mg/mL of cefovecin).

Cefadroxil – oral tablets or oral suspension

g. Route of Administration:

CONVENIA - subcutaneous injection

Cefadroxil - oral administration

To facilitate masking, dogs allocated to the CONVENIA group also received an oral placebo and dogs allocated to the cefadroxil group also received a placebo injection. Therefore, none of the individuals involved in the study (including but not limited to those individuals performing effectiveness assessments) were aware of the treatment groups.

h. Study Duration: 28 days, 42 days for those dogs requiring a second course of treatment

i. Variables Measured:

Effectiveness was assessed based on clinical signs of skin infection. Clinical signs were scored by the examining veterinarian as being absent, mild, moderate, or severe on Days 0 (prior to treatment), 7, 14, 28, and 42. At the time of the final assessment, the examining veterinarian also provided an evaluation of the overall clinical outcome of each case.

Baseline clinical pathology values (hematology, clinical chemistry, and urinalysis) were collected prior to treatment administration and at study end. Abnormal health observations and concurrent medications administered to each dog were recorded. In addition, any injection site abnormalities were recorded for each animal.

Microbiological cultures were obtained from each dog at the beginning of the study, and from any dog with a lesion to culture at the end of the study (treatment failures).

j. Statistical Analysis:

A dog successfully completed the study if each clinical sign initially classified as moderate or severe was reduced to mild or absent at the final assessment. The percentage of dogs successfully treated was calculated 28 days after administration of the final treatment. Dogs withdrawn from the study due to lack of effectiveness or adverse reactions were considered treatment failures.

The determination of effectiveness was based on the number of dogs successfully completing the study 28 days after administration of the final treatment.

A per protocol population was defined for effectiveness analysis. The per protocol population consisted of dogs that were randomized to treatment and met all of the inclusion criteria, none of the exclusion criteria, received at least one dose of either CONVENIA or cefadroxil and had sufficient observations for effectiveness evaluation.

A non-inferiority test was conducted for the percent of cases successfully treated in the two treatment groups. Non-inferiority was concluded if the one-sided lower limit of the difference between percentages of successful completion was above the non-inferiority margin of 15 percentage points. This test was conducted on the per protocol population of dogs at a one-sided 5% significance level. A secondary non-inferiority analysis was conducted excluding those cases that missed three or more doses of cefadroxil.

5. Results:

There were 320 dogs enrolled in the study. This included 157 CONVENIA cases and 163 cefadroxil cases. Eighty-five cases (85) were excluded from the effectiveness evaluation. The most common reason for exclusion was failure to confirm a viable isolate during bacterial identification and minimum inhibitory concentration testing. Other reasons for exclusion were failure to meet inclusion criteria, insufficient number of evaluable cases from a site, missing or incomplete microbiology data, and extreme scheduling deviations for the final assessment visit.

The effectiveness evaluation was based on 118 CONVENIA-treated cases and 117 cefadroxil-treated cases. This included twelve dogs (6 from each treatment group) that withdrew from the study prior to completion due to lack of effectiveness or adverse reactions. These dogs were considered treatment failures.

Among all enrolled dogs, 22 of 157 dogs in the CONVENIA group received two treatments, and 35 of 163 dogs in the cefadroxil group received two courses of treatment. Among the evaluable cases, 17 of 118 dogs in the CONVENIA group received two treatments and 26 of 117 dogs in the cefadroxil group received two courses of treatment.

The percentage of dogs from evaluable cases (CONVENIA- and cefadroxil-treated) with clinical signs of skin infection at each evaluation time point (based on each individual clinical sign) is summarized in Table 16.

Table 16: Percentage of Dogs with Clinical Signs of Skin Infections

Clinical Sign	Treatment	Day 0	Day 7	Day 14	Final Assessment
Erosion/ulceration	CONVENIA	55.9	29.6	9.6	3.6
	cefadroxil	53.8	34.5	13.2	3.6
Erythema	CONVENIA	92.4	49.6	16.7	9.0
	cefadroxil	92.3	49.1	28.9	5.5
Furuncles	CONVENIA	7.6	1.7	0.9	0.0
	cefadroxil	12.8	3.4	2.6	0.9
Nodules	CONVENIA	10.2	3.5	0.0	0.0
	cefadroxil	12.8	5.2	2.6	0.0
Papules	CONVENIA	33.9	16.5	6.1	5.4
	cefadroxil	40.2	26.7	12.3	4.5
Purulent discharge	CONVENIA	68.6	12.2	5.3	2.7
	cefadroxil	73.5	12.9	6.1	0.9
Pustules	CONVENIA	39.8	9.6	7.0	4.5
	cefadroxil	46.2	20.7	8.8	5.5
Swelling	CONVENIA	66.9	31.3	13.2	3.6
	cefadroxil	69.2	35.3	9.6	1.8

Notes:
1. Includes all evaluable dogs in the per protocol population
2. Actual study observation days for Day 0: -3 to 0, Day 7: 5 to 10, Day 14: 11 to 18, Final Assessment: Day 19 to 38 for dogs that received a single treatment and Day 36-51 for dogs that received two treatments.
3. Number of CONVENIA dogs observed on Day 0: 118; Day 7: 115 Day 14: 114, Final Assessment: 111
   Number of cefadroxil dogs observed on Day 0: 117; Day 7: 116 Day 14: 114, Final Assessment: 110
4. Some dogs were lost to failures, adverse events, and missed visits.

The percentage of dogs from evaluable cases (CONVENIA- and cefadroxil-treated) cured (each clinical sign reduced to absent) at each evaluation time point by clinical diagnosis (abscess, folliculitis, or wound) is summarized in Table 17.

Table 17: Percentage of Dogs Cured by Clinical Diagnosis

Diagnosis	Treatment	Number of Dogs	Number (Percentage[1]) of Dogs Cured		
			Day 7	Day 14	Final Assessment
Abscess	CONVENIA	29	25 (89.3)	29 (100)	27 (93.1)
	Cefadroxil	25	21 (84.0)	24 (96.0)	24 (96.0)
Folliculitis	CONVENIA	62	53 (86.9)	56 (91.8)	57 (91.9)
	Cefadroxil	67	56 (84.8)	57 (89.1)	60 (89.5)
Wound	CONVENIA	27	21 (77.8)	25 (96.1)	25 (92.6)
	Cefadroxil	25	22 (88.0)	23 (92.0)	24 (96.0)
All	CONVENIA	118	99 (85.3)	110 (94.8)	109 (92.4)
	Cefadroxil	117	99 (85.3)	104 (91.2)	108 (92.3)

Notes:

1. Percentages are based on the actual number of dogs who returned for each visit. Dogs who withdrew for apparent lack of effectiveness are counted as failures on the scheduled visits.
2. Number CONVENIA dogs observed on Day 7: 116, Day 14: 116, Final Assessment: 118. Number of cefadroxil dogs observed on Day 7: 116, Day 14: 114, Final Assessment: 117.
3. Final assessment conducted on Day 28 for dogs receiving a single treatment and on Day 42 for dogs receiving two treatments.

Twenty-eight days after initiation of the final 14-day treatment, each clinical sign of skin infection had been reduced to mild (improved) or absent (cured) in 109 (92.4 %) of CONVENIA-treated dogs and in 108 (92.3%) of cefadroxil-treated dogs.

Using a non-inferiority margin of 15%, CONVENIA was determined to be non-inferior to cefadroxil 28 days after the final injectable treatment (Table 18).

Table 18: Number and Percentage of Dogs Successfully Treated During the Study

	Number (Percentage) of Dogs Successfully Treated and Completing Study[1]	
	Final Assessment	
Treatment	Yes	No
CONVENIA	109 (92.4%)[2]	9 (7.6%)
cefadroxil	108 (92.3%)[2]	9 (7.7%)

[1]Successful completion defined as reduction in the severity of clinical signs of skin infection to mild or absent in severity.

[2] CONVENIA non-inferior to cefadroxil ($\delta = 0.15$).

Based on the clinical outcome of each case 28 days after the final injectable treatment, in the CONVENIA treatment group there were 97 (82.2%) cures,

12 (10.2%) improvements, and 9 (7.6%) failures. In the cefadroxil treatment group there were 98 (83.8%) cures, 10 (8.5%) improvements, and 9 (7.7%) failures.

a. Concomitant Treatments

A variety of medications were administered to dogs concurrently with cefovecin. These included, but were not limited to, heartworm preventatives, flea control products, sedatives/tranquilizers, anesthetic agents, routine immunizations, antihistamines, thyroid hormone supplementation, and non-steroidal anti-inflammatory agents.

b. Adverse Reactions:

Vomiting, diarrhea, decreased appetite, and lethargy were the most common abnormal observations in both treatment groups.

A total of 320 dogs were included in the field study safety analysis. Abnormal health observations reported in dogs treated with CONVENIA and cefadroxil are summarized in Table 19.

Table 19: Number of Dogs* with Adverse Reactions Reported During the Study with CONVENIA

Adverse Reactions	CONVENIA n = 157	Cefadroxil n = 163
Lethargy	2	7
Anorexia/Decreased Appetite	5	8
Vomiting	6	12
Diarrhea	6	7
Blood in feces	1	2
Dehydration	0	1
Flatulence	1	0
Increased Borborygmi	1	0

*Some dogs may have experienced more than one adverse reaction or more than one occurrence of the same adverse reaction during the study.

c. Injection Site Observations:

CONVENIA or injectable placebo was administered by the examining veterinarian subcutaneously at a site free of any pre-existing abnormalities and not near the sites of other injectable treatments. Injections were administered in five anatomical regions: thorax, forelimb, hind limb, dorsal scapula, or lumbar region. The percentage of CONVENIA-treated dogs receiving treatment at each site are as follows: thorax 24%, left and right forelimb 35%, left and right hind limb 13%, dorsal scapula 20%, and lumbar 8%. This included dogs receiving injections on Day 0 and Day 14.

There were no abnormal injection site observations in CONVENIA-treated dogs.

d. Clinical Pathology:

There were no clinically significant differences between mean values for all laboratory tests among CONVENIA and cefadroxil-treated dogs. For individual laboratory values the following findings were noted:

Eight CONVENIA-treated dogs had normal gamma glutamyl transferase (GGT) levels pre-study (normal range: 0 - 10 IU/L) and elevated levels post-study (range 11 - 21 IU/L).

Four CONVENIA-treated dogs had normal alanine aminotransferase (ALT) levels pre-study (normal range: 0 - 120 IU/L) and elevated levels post-study (range 134 - 454 IU/L).

Four CONVENIA-treated dogs had normal ALP levels pre-study (normal range: 21 - 125 IU/L) and elevated ALP levels post-study (range 136 - 144 IU/L).

Seven CONVENIA-treated dogs had normal platelet counts pre-study (normal range: 2-5 x 10^5/mm^3) and decreased platelet counts post-study (range 1.4 to 1.9 x 10^5/mm3). One CONVENIA-treated dog had a pre-study platelet count of 1.9 x 10^5/mm^3, a post-study count of 0.4 x 10^5/mm^3, and giant platelets were observed on the blood smear. In this animal, the red blood cell count was below normal both pre- and post-study but increased slightly from 4.76 to 5.07 x 10^6/mm^3 over the course of the study (normal range 5.5 - 8.5 x 10^6/mm^3). Clinical manifestations of thrombocytopenia were not documented.

e. Microbiology:

CONVENIA is a cephalosporin antibiotic. Like other β-lactam antimicrobials, CONVENIA exerts its inhibitory effect by interfering with bacterial cell wall synthesis. This interference is primarily due to its covalent binding to the penicillin-binding proteins (PBPs) (i.e., transpeptidase and carboxypeptidase), which are essential for synthesis of the bacterial cell wall. For *E. coli*, the *in vitro* activity of CONVENIA is comparable to other cephalosporins, but due to the high-affinity protein-binding, the *in vivo* free concentration of cefovecin does not reach the MIC_{90} for *E. coli* (1.0 mcg/mL). CONVENIA is not active against *Pseudomonas* spp. and enterococci.

Identification of bacterial pathogens was made to the species level, based on morphology, Gram stain, growth characteristics, standard individual

biochemical testing, and/or commercially available identification test kits. Minimum inhibitory concentration (MIC) testing was conducted in accordance with applicable Clinical and Laboratory Standards Institute (CLSI) standards. CONVENIA MICs for the pre-treatment bacterial pathogens isolated from enrolled dogs are summarized in Table 20.

Table 20: Activity of CONVENIA Against Pathogens Isolated from Dogs Treated With CONVENIA in Field Studies in the U.S. During 2001-2003

Disease	Pathogen	Microbiological Treatment Outcome	Number of Isolates	Sample Collection (Time Relative to Treatment)	MIC_{50} µg/mL	MIC_{90} µg/mL	MIC Range µg/mL
Skin infections	*Staphylococcus intermedius*	Success	44	Pre-Treatment	0.12	0.25	≤ 0.06 - 2
		Failure	4	Pre-Treatment			0.12 - 2
	Streptococcus canis (Group G)	Success	16	Pre-Treatment	≤ 0.06	≤ 0.06	≤ 0.06
		Failure	2	Pre-Treatment			≤ 0.06

6. Conclusions:

CONVENIA administered as a subcutaneous injection at a dose of 3.6 mg/lb (8 mg/kg) body weight was effective for the treatment of skin infections (superficial secondary pyoderma, abscesses, and wounds) in dogs caused by susceptible strains of *Staphylococcus intermedius* and *Streptococcus canis* (Group G). Twenty-two CONVENIA-treated dogs required two injections.

VI. TARGET ANIMAL SAFETY:

A. Drug Tolerance Study:

1. Type of Study: Laboratory safety study (GLP)

2. Study Director: Michael C. Savides, PhD.
Ricerca, LLC
Concord, OH

3. General Design:

a. Purpose: To determine the toxic effects of CONVENIA when administered once subcutaneously to dogs at an exaggerated dose (180 mg/kg body weight).

b. Test Animals: Twelve healthy Beagle dogs (6M and 6F), approximately seven months of age, were randomly assigned to one of two groups. Six dogs (3/sex) were randomly assigned to the CONVENIA group and six dogs (3/sex) were randomly assigned to the control group.

c. Control: Injectable Sodium Chloride (0.9% sterile)

d. Dosage form: Final market formulation, 80 mg/mL of injectable CONVENIA

e. Route of administration: dorsoscapular subcutaneous injection

f. Dosages used:

Treatment Groups for the Drug Tolerance Study

Group	Dose mg/kg	Number and Sex of Dogs
1	0 mg/kg (saline)	3 males, 3 females
2	180 mg/kg	3 males, 3 females

g. Test duration: Thirty days

h. Variables measured: Clinical observations, physical exams, injection site evaluations, body weights, hematology, serum chemistry, coagulation tests, plasma drug concentrations, urinalysis, and food consumption were assessed.

4. Results: All dogs survived to termination of the study.

a. Abnormal clinical findings included irritation, scratching/chewing at the injection site and vocalization following administration in four CONVENIA-treated dogs and three control dogs. Edema ventral to the injection site was observed in six CONVENIA-treated dogs and three control dogs during the first 8 hours post-dosing. All edema resolved within 24 hours of dosing. One CONVENIA-treated dog vomited on Day 23 of the study, with no other clinical abnormalities noted.

b. Hematology: There was a trend for the APTT (activated partial thromboplastin time) values to be higher in the CONVENIA-treated group compared to the control group, although all values remained within the reference range used for this study[2.]

c. Clinical chemistry evaluations showed higher mean alkaline phosphatase values for the CONVENIA-treated dogs on Days 10 and 30 compared to the control dogs. All values stayed within the normal reference range.

d. Plasma drug concentrations: In both male and female animals, concentrations of CONVENIA were greatest at the initial sampling time (1.5 hours), and remained above the limit of detection (0.05 µg/ml) for the

[2] Duncan, J. R., Prasse K. W. Veterinary Laboratory Medicine Clinical Pathology, 2nd edition, 1986.

duration of the study. These data indicate that CONVENIA was rapidly absorbed and that there was a prolonged time for elimination from the plasma.

5. Conclusions: Under the conditions of this study, the dogs remained healthy throughout the 30-day duration. Irritation following injection and transient injection site edema occurred in both the control and CONVENIA-treated dogs. The edema resolved within 24 hours.

B. Margin of Safety and Injection Site Tolerance of Cefovecin Injectable Solution in Dogs:

1. Type of Study: Laboratory safety study (GLP)

2. Study Director: Elizabeth Evans, DVM
Midwest Research Institute (MRI)
Kansas City, MO

3. General Design:

a. Purpose: To evaluate the safety and injection site toleration of CONVENIA when administered subcutaneously once every 7 days for a total of five injections in dogs.

b. Test Animals: Thirty-two healthy Beagle dogs (16M and 16F), approximately 4 months of age, were randomly assigned to the four dose groups.

c. Control: Injectable Sodium Chloride (0.9% sterile)

d. Dosage form: Final market formulation, 80 mg/mL of CONVENIA

e. Route of administration: dorsoscapular subcutaneous injection

f. Dosages used:

Treatment Groups for Safety Study

1) Control (saline) every seven days for four consecutive weeks (5 total doses)
2) 12 mg/kg (1.5 X) every seven days for four consecutive weeks (5 total doses)
3) 36 mg/kg (4.5 X) every seven days for four consecutive weeks (5 total doses)
4) 60 mg/kg (7.5 X) every seven days for four consecutive weeks (5 total doses)

g. Test duration: Forty-two days

h. Variables measured: Evaluations included clinical signs, general health observations, physical examinations, body weight, hematology, coagulation tests, serum chemistry, urinalysis, fecal examination, gross pathology and histopathology, injection site evaluations, and plasma blood concentrations.

4. Results: All dogs survived to termination of the study.

a. Clinical observations: There were observations of red and inflamed ears of dogs in all study groups. This occurrence may have been related to husbandry conditions, and resulted in 63 occurrences in the control group, 77 occurrences in the 12 mg/kg (1.5 X) group, 76 occurrences in the 36 mg/kg (4.5 X) group, and 135 occurrences in the 60 mg/kg (7.5 X) group.

Alopecia was reported in several dogs among all groups throughout the study, and was attributed by the study veterinarian to traumatic rubbing.

Other abnormal clinical findings included seven CONVENIA-treated dogs with red scleras at Day 7. Throughout the study there was one case of soft stool in the control group, two cases in the 36 mg/kg group, and one case in the 60 mg/kg group. There was one incidence of vomiting in the control group, two cases in the 12 mg/kg group, three in the 36 mg/kg group, and five cases in the 60 mg/kg group. Additionally, a 60 mg/kg dog with an elevated temperature and panting was noted on Day 27. No other problems were noted in this dog.

b. Hematology: Generally, for all four groups in the study, the prothrombin time (PT) was shorter (6 - 7 seconds) than the reference range used in this study (13.2 - 22 seconds).[3] Although all groups ran low for the given range, the mean prothrombin time in the 60 mg/kg group males was significantly ($p = 0.0010$) longer than that of the control group.

There were statistically significant differences among treatment groups for white blood cell (WBC) counts. There was significant interaction between the treatment and the time period. The mean values for all the treated groups were statistically significantly lower than the control group at the first, third, fourth and fifth time points. (Time 0 = pre-study, Time 1 = Days 6 - 7, Time 2 = Days 12 - 13, Time 3 = Days 19 - 21, Time 4 = Days 26 - 28, and Time 5 = Days 40 - 41 of the study.) The mean WBC counts for the 36 mg/kg group ($p = 0.0324$), the mean neutrophil count for the 12 mg/kg group ($p = 0.0416$) and the 36 mg/kg group ($p = 0.0787$) were significantly lower than the control group at the second time point.

[3] Bonagura, JD. 1995. Kirk's Veterinary Therapy XII: Small Animal Practice. W.B. Saunders Co., Philadelphia.

c. Serum Chemistry: There were statistically significant differences amongst the treated groups for bile acid values. The mean bile acid values for the 12 mg/kg group (p = 0.0899) and the 60 mg/kg group (p = 0.0040) were statistically significantly higher than that of the control group.

The mean BUN value for the 36 mg/kg group was statistically significantly higher (p = 0.0088) than that of the control group.

d. Injection site evaluations:

Whining and discomfort were noted in two 60 mg/kg dogs during or after dosing on Day 7. Swelling following injections usually appeared by one hour post-administration. The number of animals that showed swellings after each injection for each treatment group is represented in the Table 21. Fisher's exact test was used to test the difference between the control and the treated groups for each injection time.

Table 21: Number of Dogs/Group with Injection Site Swelling

	Control	12 mg/kg	36 mg/kg	60 mg/kg
1st injection	1	1	6*	5
2nd injection	4	3	7	8*
3rd injection	4	3	7	7
4th injection	3	3	7	8*
5th injection	2	4	3	7*

* p = < 0.1, statistically significant

A statistically significant number of animals in the 60 mg/kg group showed swellings after each injection compared to the control group following the 2nd, 4th, and 5th injection periods. Also, a statistically significant number of animals in 36 mg/kg group showed swellings compared to the control group following the 1st injection. The maximum swelling measured throughout the study was 6 mm X 6 mm (length X width). Histopathology of the injection sites included 1 erosion/ulcer in the epidermis of one control dog, three 12 mg/kg dogs, four 36 mg/kg dogs, and four 60 mg/kg dogs.

e. Pathology: There was one dog in the 60 mg/kg group that exhibited glomerulopathy on histopathology. There were five treated dogs (one-12 mg/kg dog, one-36 mg/kg dog, and three-60 mg/kg dogs) and two control dogs that exhibited mild lamina propria and/or GALT (gastrointestinal associated lymphoid tissue) hemorrhage along the intestinal tract on histopathology. There was a male in the 60 mg/kg group that had minimal peliosis hepatis.

f. Plasma drug concentrations: A less than dose proportional change in total drug exposure was seen as doses increased from 12 mg/kg to 60 mg/kg in dogs. Accordingly, total drug peak and trough concentrations of CONVENIA in plasma were similar in dogs receiving subcutaneous doses of 12 mg/kg, 36 mg/kg, and 60 mg/kg of CONVENIA. Concentrations were similar between male and female dogs.

5. Conclusions: An adequate safety margin was demonstrated for CONVENIA when administered under the conditions of this study throughout the 42-day study duration. Occurrences of injection site swellings increased with increasing doses of CONVENIA and usually appeared within one hour of administration. Mild hepatic and renal lesions were observed in two of the 60 mg/kg group dogs.

VII. HUMAN FOOD SAFETY:

This drug is intended for use in cats and dogs, which are non-food animals. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

VIII. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to CONVENIA:

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. Consult a physician in case of accidental human exposure. 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 cefovecin, are advised to avoid direct contact of the product with the skin and mucous membranes”.

The following items were examined to ensure human user safety: the material safety data sheet (MSDS) for cefovecin and the data submitted in support of this NADA. According to the MSDS for the active ingredient (dated September 13, 2007, Pfizer), the active ingredient may cause allergic skin reaction upon contact. The above Human Warnings should adequately address this concern.

IX. 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.

The data demonstrate that CONVENIA, when used according to the label, is safe and effective for the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of *Pasteurella multocida.*

The data also demonstrate that CONVENIA, when used according to the label, is safe and effective for the treatment of skin infections (secondary superficial pyoderma, abscesses, and wounds) in dogs caused by susceptible strains of *Staphylococcus intermedius* and *Streptococcus canis* (Group G).

A. Marketing Status:

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 cats and dogs, treatment of these conditions, and monitoring for possible adverse reactions of the drug.

B. Exclusivity:

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 approval because no active ingredient of the new animal drug has previously been approved.

C. Patent Information:

U.S. Patent Number	Date of Expiration
6,020,329	July 22, 2011

X. ATTACHMENTS:

Facsimile Labeling:
Package insert
Vial
Carton