

## FREEDOM OF INFORMATION SUMMARY

### I. GENERAL INFORMATION

#### A. File Number

NADA 140-684

#### B. Sponsor

Fort Dodge Laboratories, Inc.  
Div. of American Home Products Corp.  
800 5th St., NW  
Fort Dodge, IA 50501-0508

#### C. Proprietary Name

CEFA-DROPS (cefadroxil) Veterinary Powder for Oral Suspension

#### D. Product Established Name

cefadroxil

#### E. Dosage

**Dogs:** 10 mg/lb twice daily

**Cats:** 10 mg/lb once daily

Tap bottle lightly to loosen powder. Add 10.4 ml of water in two portions. Shake well after each addition. After mixing, store in refrigerator. Shake well before use. Discard unused portion after 14 days.

When mixed as directed, each ml contains 50 mg cefadroxil activity. The dropper supplied with CEFA-DROPS is calibrated to deliver 0.25 ml (12.5 mg), 0.5 ml (25 mg), 0.75 ml (37.5 mg) and 1.0 ml (50 mg).

#### F. Indications for Use

CEFA-DROPS (cefadroxil) is indicated for the treatment of the following conditions:

**Dogs:** Genitourinary tract infections (cystitis) caused by susceptible strains of *Escherichia coli*, *Proteus mirabilis*, and *Staphylococcus aureus*. Skin and soft tissue infections including cellulitis, pyoderma, dermatitis, wound infections and abscesses caused by susceptible strains of *Staphylococcus aureus*.

**Cats:** Skin and soft tissue infections including abscesses, wound infections, cellulitis and dermatitis caused by susceptible strains of *Pasteurella multocida*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Streptococcus* spp.

### II. EFFECTIVENESS

The effectiveness of cefadroxil for the indications listed above has been demonstrated and approved (NADA 119-688) using the tablet formulation in dogs (September 17,

1982, October 26 1984 and April 14, 1987) and cats (February 3, 1986) as described in Freedom of Information Summaries released on those dates. The relevance of those data to the present application was demonstrated in the following studies.

#### **A. Pivotal Bioequivalency Studies in Dogs and Cats**

##### **1) Investigator:**

Dr. John G. Babish, PhD  
University of California  
Davis, California 95616

##### **2) General Design of the Investigation:**

The purpose of the studies was to determine whether the proposed oral powder formulation of cefadroxil is bioequivalent to the approved tablet formulations in both dogs and cats. This was determined by giving each formulation orally at the approved dosage of 10 mg/lb following a crossover experimental design and comparing the serum concentration vs time profiles and other pharmacokinetic parameters.

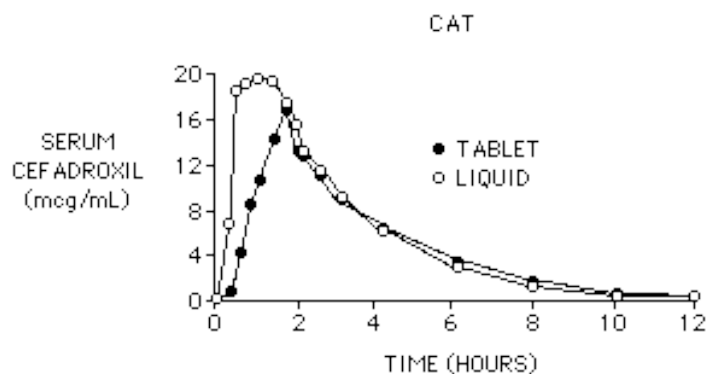
Test animals were 12 mature Beagle dogs, of both sexes, in one study, and 12 mature domestic shorthair cats, of both sexes, in a second. In each study, animals were randomly divided into two subgroups of six each for crossover treatment purposes. Subgroup A received the tablet formulation first followed one week later by the liquid formulation, while subgroup B received the liquid formulation first.

The control treatment was the approved formulation of cefadroxil film coated tablets, while the test dosage form was cefadroxil powder for oral suspension, equivalent to the formulation to be marketed, both administered orally at the approved dosage of 10 mg/lb body weight.

Pertinent parameters measured were cefadroxil concentrations determined by standard microbiological assay methods on blood serum samples collected at predetermined intervals following each treatment.

##### **3) Results**

Comparisons of the cefadroxil serum concentration time profiles between liquid and tablet formulations in both dogs and cats are illustrated graphically below. These curves were derived by plotting the average actual concentration (n = 12) against the average actual sampling time.



No adverse reactions of any kind were noted in either dogs or cats given either formulation.

Absorption and elimination rate constants were calculated for each individual animal by mathematical curve fitting of its data points. Area under the curve was calculated by the trapezoid method, peak concentration was defined as the highest concentration detected and time to peak was defined as the time at which that concentration was measured, all calculated from actual concentrations measured at actual sampling times. The following pharmacokinetic parameters were thus calculated:

| ANIMAL | PARAMETER                                         | AVERAGE (n=12)<br>TABLETS | AVERAGE (n=12)<br>LIQUID |
|--------|---------------------------------------------------|---------------------------|--------------------------|
| DOG    | absorption rate constant<br>(min <sup>-1</sup> )  | .0308                     | .0393                    |
| DOG    | elimination rate constant<br>(min <sup>-1</sup> ) | .0052                     | .0055                    |
| DOG    | area under curve (mcg x<br>min)/ml                | 4900.4                    | 4699.3                   |
| DOG    | time to peak concentration<br>(min)               | 125.8                     | 87.1                     |
| DOG    | peak concentration<br>(mcg/ml)                    | 19.8                      | 22.0                     |
| CAT    | absorption rate constant<br>(min <sup>-1</sup> )  | .0325                     | .0534                    |
| CAT    | elimination rate constant<br>(min <sup>-1</sup> ) | .0069                     | .0077                    |
| CAT    | area under curve (mcg x<br>min)/ml                | 3424.5                    | 4027.4                   |
| CAT    | time to peak concentration<br>(min)               | 116.4                     | 68.3                     |
| CAT    | peak concentration<br>(mcg/ml)                    | 17.4                      | 22.3                     |

#### 4) Conclusions

No differences were found in the abilities of cats and dogs to absorb cefadroxil from either the tablet or liquid formulation. In cats the calculated area under the curve was numerically larger for the liquid formulation than for the tablets,

indicating a slightly greater bioavailability of cefadroxil from the liquid formulation. In both dogs and cats, a shorter time was required for cefadroxil to reach peak blood concentrations from the liquid formulation than from the tablets. This was anticipated since the tablets had to undergo disintegration before cefadroxil could be absorbed.

## **B. Pivotal Clinical (field) Study**

### **1) Title:**

Clinical Evaluation of Cefadroxil Oral Suspension for the Treatment of Cystitis in the Dog and Skin and Soft Tissue Infections in Dogs and Cats.

### **2) Investigators:**

Eleven licensed veterinarians engaged in companion animal practice participated in the clinical trial:

Dr. Randall Bradshaw  
Waterlick Plaza  
Lynchburg, VA 24502

Dr. Steven Bruck  
4240 Slate Hill Rd  
Marcellus, NY 13108

Dr. Wayne Carter  
Georgetown Rd  
Charlottesville, VA 22901

Dr. Dale Eckert  
Lexington Rd., Box 108  
Versailles, KY 40383

Dr. Nancy Freeborough  
120 Julian Plaza  
Syracuse, NY 13210

Dr. John Gruss  
Box 67  
Earlsville, VA 22936

Dr. Mark Lowe  
Rt 1, Box 46G  
Homosassa, FL 32646

Dr. Carol Moon  
9758 Gayton Rd  
Richmond, VA 23233

Dr. Albert Smith  
3050 Berkmar Dr  
Charlottesville, VA 22901

Dr. Robert Stein  
2217 Kensington Ave.  
Snyder, NY 14226

Dr. Charles H. Wood, Jr.  
McIntire Plaza  
Charlottesville, VA 22901

### **3) General Design of the Investigation**

The purpose of the study was to compare the safety and effectiveness of cefadroxil given as an oral suspension formulation with that of the previously approved film coated tablets under conditions of veterinary practice.

Test animals were dogs of either sex and any age weighing up to 20 pounds that were presented to the practicing veterinarian for treatment of either urinary tract infections or skin and soft tissue infections, and cats of either sex and any age that were presented for treatment of skin and soft tissue infections.

Controls in this study were dogs and cats treated with the approved tablet formulation of cefadroxil (active treatment control).

Diagnosis of urinary tract infections was made by physical examination and by urinalysis and bacteriologic culture of samples obtained by cystocentesis (aseptically placing sterile needle through abdominal wall into bladder and withdrawing urine sample). Diagnosis of skin and soft tissue infections was made by physical examination, including drawing lesion(s) on schematic diagrams provided, and by bacteriologic culture.

Dosage forms, route, and dosage were cefadroxil powder for oral suspension which, when reconstituted according to directions, provided 50 mg cefadroxil activity per ml, and cefadroxil 50 mg film coated tablets, given orally at the approved dosage of 10 mg/pound twice daily to dogs and once daily to cats.

Pertinent parameters measured included comparison of pretreatment and post treatment results of physical examination, microbiological culture of lesions in skin infection cases, and urinalysis and culture of urine samples obtained by cystocentesis. Post treatment cultures were taken approximately seven days after last treatment with cefadroxil. Investigators were also asked to give an overall evaluation of response to therapy on an "excellent", "good", "fair" or "poor" basis.

### **4) Results**

A total of 148 animals were entered into the study of which 144 were evaluable, comprised of 99 cats and 45 dogs. Of the 99 cats, 55 were treated with the cefadroxil liquid formulation and 44 with approved cefadroxil tablets. Of the 45 dogs, 22 were treated with the liquid and 23 received the tablet formulation. All of the cats and 36 of the dogs were treated for skin and soft tissue infections, while the remaining nine dogs were treated for urinary tract infections.

Clinically, both formulations of cefadroxil were found to be effective in relieving signs of skin infections in cats and dogs as well as cystitis in dogs. The microbiological results are summarized in the following table:

**Number of Isolates Before & After Treatment with Cefadroxil**

| PATHOGEN                     | LIQUID<br>-PreRx | LIQUID<br>-PostRx | LIQUID<br>-%elim | Tablet<br>-PreRx | Tablet<br>-PostRx | LIQUID<br>-%elim |
|------------------------------|------------------|-------------------|------------------|------------------|-------------------|------------------|
| <i>Staphylococcus aureus</i> | 24               | 4                 | 83               | 27               | 2                 | 99               |
| <i>Pasteurella multocida</i> | 14               | 1                 | 93               | 11               | 0                 | 100              |
| <i>Escherichia coli</i>      | 7                | 1                 | 86               | 5                | 1                 | 80               |
| <i>Streptococcus</i><br>spp. | 12               | 0                 | 100              | 8                | 0                 | 100              |
| All Organisms                | 105              | 6                 | 94               | 95               | 3                 | 97               |

The investigator's overall evaluations of the response to treatment are summarized in the following table:

**no. "excellent" or "good" / total (%)**

| CLAIM                   | LIQUID      | TABLET      |
|-------------------------|-------------|-------------|
| Cat, skin infections    | 50/55 (91%) | 42/44 (95%) |
| Dog, skin infections    | 17/18 (94%) | 17/18 (94%) |
| Dog, urinary infections | 4/4 (100%)  | 3/5 (60%)   |

**5) Statistical Analysis**

Statistical analysis was not deemed necessary to evaluate the results of this study since the results by all criteria are clearly similar between animals given cefadroxil as liquid or as tablets.

**6) Conclusions**

Results of the study demonstrate the acceptability of cefadroxil powder for oral suspension for treatment of dogs and cats, and demonstrate that safety and effectiveness of the cefadroxil liquid are equivalent to that of the approved tablet formulation, when tested under conditions of veterinary practice.

**7) Adverse Reactions**

No unexpected side effects were encountered in animals treated with either dosage form. Diarrhea was reported in one cat treated with liquid and two cats treated with tablets. Vomiting was reported in one cat in each group and lethargy was noted in one cat of the tablet group. No side effects were reported in dogs.

**C. Corroborative Bioavailability Study**

**1) Title: A Comparison of Oral Bioavailability of Cefadroxil Tablets, Capsules and Suspension**

**2) Investigator:**

Dr. Mark Strauch  
The Ohio State University

College of Veterinary Medicine  
Columbus, Ohio

**3) Methods:**

Six healthy adult hound type dogs of both sexes were sequentially given cefadroxil formulated as tablets, capsules, suspension and intravenous solution, each at the approved table dosage of 22 mg/kg (10 mg/lb). Serum samples were collected before and at prescribed intervals following dosage, frozen, and later analyzed for cefadroxil activity by an HPLC procedure. Additionally, 24 hour urine collections were made on dogs given the drug intravenously, and percent binding to serum protein was also determined. Pharmacokinetic parameters determined following oral administration of the respective formulations and intravenous injection were compared.

**4) Results: Mean values for pharmacokinetic parameters are given below.**

| Parameter                                      | tablets | suspension | capsules |
|------------------------------------------------|---------|------------|----------|
| elimination rate constant (min <sup>-1</sup> ) | .0072   | .0051      | .0068    |
| area under curve (mcg x min/ml)                | 2940    | 4248       | 3768     |
| time to peak concentration (min)               | 70      | 100        | 123      |
| peak concentration (mcg/ml)                    | 17.4    | 14.9       | 18.6     |

Results of urinary recovery studies revealed that an average of 39% of the intravenous dose of cefadroxil was recovered within 24 hours from the dogs. Protein binding averaged 25%.

**III. ANIMAL SAFETY:**

The safety of cefadroxil has been demonstrated and approved (NADA 119-688) using the tablet formulation in both dogs (September 17, 1982) and cats (February 3, 1986) as described in Freedom on Information summaries released on those dates. The relevance of those data to the present application was demonstrated by results of the pivotal bioequivalency and clinical data described above.

**IV. HUMAN SAFETY:**

Data on human food safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. The drug is labeled for use in dogs and cats only, which are non-food animals.

In regards to human safety relative to possession, handling and administration of the drug, no special caution statement is needed.

**V. AGENCY CONCLUSIONS:**

The data submitted in support of this NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. It demonstrates that CEFA-DROPS (cefadroxil, 50 mg/ml) Veterinary Powder for Oral Suspension is safe and effective for the label indications when used in accordance with the labeling directions.

Differential diagnosis and monitoring of the progress of patients require the professional expertise of a veterinarian. The Agency, therefore, concluded that CEFA-

DROPS Veterinary Powder for Oral Suspension should be provided to the public on a prescription basis.

## **VI. ATTACHMENTS**

Determinative and Confirmatory Method (if applicable)

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