

Date of Approval: December 16, 2014

FREEDOM OF INFORMATION SUMMARY
SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-232

SIMPLICEF

Cefpodoxime proxetil

Chewable tablets

Dogs

This supplement provides for the addition of a flavored, chewable tablet.

Sponsored by:

Zoetis, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-232

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

SIMPLICEF

D. Established Name

Cefpodoxime proxetil

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Chewable tablet

G. Amount of Active Ingredient

100 mg tablets, 200 mg tablets

H. How Supplied

100 mg scored tablets in 100 count bottles and 250 count bottles
200 mg scored tablets in 100 count bottles and 250 count bottles

I. Dispensing Status

Rx

J. Dosage Regimen

The dose range of SIMPLICEF (cefpodoxime proxetil) Chewable 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.

K. Route of Administration

Oral

L. Species/Class

Dog

M. Indication

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

N. Effect of Supplement

This supplement provides for the addition of a flavored, chewable tablet.

II. EFFECTIVENESS

Refer to the original Freedom of Information (FOI) Summary for SIMPLICEF tablets (NADA 141-232) for the effectiveness studies used to support the original approval. The effectiveness for SIMPLICEF Chewable tablets has been demonstrated via bioequivalence to the original SIMPLICEF tablets.

A. Dosage Characterization

This supplemental approval does not change the previously approved dose range. The FOI Summary for the original approval of NADA 141-232, dated July 22, 2004, contains dosage characterization information for the 5-10 mg/kg dose once a day in dogs for 5 to 7 days, or for 2 to 3 days beyond the cessation of clinical signs, up to a maximum of 28 days.

B. Substantial Evidence

1. Fed Bioequivalence Study: Comparative pharmacokinetic study of SIMPLICEF tablet and a chewable cefpodoxime proxetil tablet following oral administration in fed female Beagle dogs (i.e., Dose Confirmation, Clinical Field Study, Pharmacokinetics, Microbiology, etc.)
 - a. Type of Study: Pharmacokinetic study
 - b. Testing Facility: Southwest Bio-labs, Las Cruces, NM.
 - c. General Design:
 - (1) Purpose of Study: This pharmacokinetic study was conducted to demonstrate the bioequivalence of the current SIMPLICEF film coated tablet and the chewable cefpodoxime proxetil tablet in fed dogs following oral administration.
 - (2) Study Design: This study was a three-sequence, three-period, two-treatment crossover pharmacokinetic study.
 - (3) Description of Test Animals: Thirty (30) healthy, female Beagles, over 9 months of age and weighing 8.2 to 12.8 kg, were used in the study.
 - (4) Dosage Form: SIMPLICEF film coated tablets and chewable cefpodoxime proxetil tablets

- (5) Prandial State: Dogs were fasted overnight (>8 hours) and then fed their daily food ration approximately 30 minutes before dosing.
- (6) Route of Administration: The whole tablets were administered as a single oral dose by hand by placing the tablet near the back of the mouth followed by an oral flush with water to facilitate passage of the dose to the stomach.
- (7) Dose Rate: 100 mg cefpodoxime free acid equivalents
- (8) Assay Methodology: The concentration of cefpodoxime in plasma was measured using a validated LC-MS/MS assay.

d. Results:

- (1) The following least squares mean PK values were determined for SIMPLICEF tablets and the chewable tablet, respectively: C_{max} , 44.5 and 44.3 $\mu\text{g/mL}$; and $AUC_{0-t(\text{last})}$, 336 and 328 $\mu\text{g}\cdot\text{h/mL}$.
- (2) The standard bioequivalence limits of 80% to 125% for the 90% confidence limit were used. $AUC_{0-t(\text{last})}$ and C_{max} for the SIMPLICEF tablets and the new chewable tablet were found to be bioequivalent. The 90% confidence intervals for the ratios of these parameters were contained within 80% to 125% (Table 1).

Table 1. Bioequivalence analysis for SIMPLICEF Chewable tablets to SIMPLICEF tablets following oral administration to dogs.

PK parameter	Contrast	Ratio of LS-mean	90% confidence limits	Bioequivalent*
$AUC_{0-t(\text{last})}$	Chewable tablet/tablet	101%	98.8% - 104%	Yes
C_{max}	Chewable tablet/tablet	99.5%	91.5% - 108%	Yes

*Bioequivalent if the upper and lower bounds of the 90% confidence limits are within 80-125%.

- e. Adverse events: One dog that vomited profusely and became pruritic with urticaria was removed from the study prior to Period 3 due to a possible drug reaction. The dog recovered.
- f. Conclusions: SIMPLICEF tablets and SIMPLICEF Chewable tablets were bioequivalent following oral administration to fed dogs. The LS means for both $AUC_{0-t(\text{last})}$ and C_{max} ratios had 90% confidence limits that were within 80 - 125%, meeting the bioequivalence criteria.

2. Fasted Bioequivalence Study: Comparative pharmacokinetic study of SIMPLICEF tablet and a chewable cefpodoxime proxetil tablet following oral administration in fasted male and female Beagle dogs.
 - a. Type of Study: Pharmacokinetic study
 - b. Testing Facility: Advinus, Bangalore, India
 - c. General Design:
 - (1) Purpose of Study: This pharmacokinetic study was conducted to demonstrate the bioequivalence of the original approved SIMPLICEF tablet and a chewable cefpodoxime proxetil tablet in fasted dogs following oral administration.
 - (2) Study Design: This study was a three-sequence, three-period, two-treatment crossover pharmacokinetic study.
 - (3) Description of Test Animals: Thirty (30) healthy Beagles (15 male and 15 female), aged 9 months to 5 years and weighing 8.2 to 15.8 kg, were used in the study.
 - (4) Dosage Form: SIMPLICEF film coated tablets and chewable cefpodoxime proxetil tablets
 - (5) Prandial State: Dogs were fasted overnight prior to dosing and food was returned 4 hours post-dose.
 - (6) Route of Administration: The whole tablets were administered as a single oral dose by hand by placing the tablet near the back of the mouth followed by an oral flush with water to facilitate passage of the dose to the stomach.
 - (7) Dose Rate: 100 mg cefpodoxime free acid equivalents
 - (8) Assay Methodology: The concentration of cefpodoxime in plasma was measured using a LC-MS/MS assay.
 - d. Results: The study design and protocol allowed for the use of scaled bioequivalence because of the cefpodoxime pharmacokinetic variability. For the dosage forms to be determined bioequivalent using scaled bioequivalence, the within animal standard deviation of C_{max} or $AUC_{0-t(last)}$ must be >0.294 , the upper 95% confidence bound must be <0 , and the geometric mean ratio (Chewable tablet/tablet) must be between 0.80 and 1.25. $AUC_{0-t(last)}$ did not meet the protocol criteria for scaled bioequivalence. The within animal standard deviation was <0.294 , and therefore the standard bioequivalence limits of 80% to 125% for the 90% confidence limits were used.

The standard bioequivalence criteria for $AUC_{0-t(last)}$ was met (Table 2). The scaled bioequivalence approach was used for C_{max} since the within animal variability was 0.444. The scaled bioequivalence criteria for C_{max} was met with the 95% upper confidence bound of -0.08 and the geometric mean ratio of 1.11 (Table 3).

Table 2. Bioequivalence analysis for SIMPLICEF Chewable tablets and SIMPLICEF tablets following oral administration to dogs.

PK parameter	Contrast	Ratio of LS means	90% confidence limits	Bioequivalent*
AUC _{0-t(last)}	Tablet/Chewable tablet	103%	94.1 – 112%	Yes

*Bioequivalent if the upper and lower bounds of the 90% confidence limits are within 80-125%.

Table 3. Bioequivalence analysis for SIMPLICEF Chewable tablets to SIMPLICEF tablets following oral administration to dogs.

PK parameter	Chewable tablet/tablet geometric mean ratio	Upper 95% confidence bound	Within animal SD	Within animal CV	Scaled Bioequivalent*
C _{max}	1.11	-0.08	0.444	0.47	Yes

*If within animal standard deviation (SD) > 0.294, then use scaled BE. If upper 95% confidence bound < 0 and the ratio is between 0.80 and 1.25, then conclude bioequivalent.

- e. Conclusions: The SIMPLICEF Chewable tablet and the SIMPLICEF tablet met the bioequivalence criteria for the AUC_{0-t(last)} and C_{max} when administered orally to fasted dogs.

3. Comparative Dissolution Profiles:

- a. The dissolution profiles of the SIMPLICEF tablets and the SIMPLICEF Chewable tablets were completed using the USP cefpodoxime proxetil tablet method.
- b. Results: The 100 mg SIMPLICEF tablets, the 200 mg SIMPLICEF tablets, the 100 mg SIMPLICEF Chewable tablets, and the 200 mg SIMPLICEF Chewable tablets all had mean drug release greater than 85% in 15 minutes, which demonstrates similar dissolution for the 200 mg and 100 mg tablets, as only the 100 mg tablets were used in the above bioequivalence studies.

III. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-232, dated July 22, 2004, contains a summary of target animal safety studies that demonstrate safety of SIMPLICEF tablets for the 5-10 mg/kg dose once a day in dogs for 5 to 7 days, or for 2 to 3 days beyond the cessation of clinical signs, up to a maximum of 28 days.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. 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.

V. USER SAFETY

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

Not for human use. Keep this and all drugs out of reach of children and pets. 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.

VI. 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 SIMPLICEF Chewable tablets when used according to the label, is safe and effective for the treatment of skin infections (wounds and abscesses) in dogs caused by susceptible strains of *Staphylococcus pseudintermedius*, *Staphylococcus aureus*, *Streptococcus canis* (group G, β hemolytic), *Escherichia coli*, *Pasteurella multocida*, and *Proteus mirabilis*.

A. Marketing Status

This 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.

B. Exclusivity

SIMPLICEF Chewable tablets, as approved in our approval letter, does not qualify for marketing exclusivity under section 512(c)(2)(F) of the Federal Food, Drug, and Cosmetic Act.

C. Supplemental Applications

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(1) or (2)).

D. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.