PIEDMONT
ANIMAL HEALTH

2013 AUG 13 A 10:25

August 12, 2013

Dockets Management Branch, HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: ANADA Suitability Petition

Dear Dr. Harshman:

Enclosed please find a Suitability Petition submitted in accordance with section 512 (n)(3) of the Federal Food, Drug and Cosmetic Act on behalf of the sponsor, Piedmont Animal Health, 204 Muirs Chapel Road Suite 200, Greensboro, NC 27301, USA.

The Sponsor requests through this Suitability Petition permission to file an Abbreviated New Animal Drug Application (ANADA) for a generic new animal drug cefpodoxime proxetil soft chewable tablet which differs from the pioneer product, SIMPLICEF™ (cefpodoxime proxetil) tablet approved under NADA 141-232 (Pharmacia and Upjohn Company, Division of Pfizer, Inc.), by the following characteristic: a film-coated tablet versus a soft chewable tablet. The generic product will be a soft chewable round, scored tablet, whereas the pioneer product is an elliptical, scored tablet (100 mg) and a round rectangle, scored tablet (200 mg). The generic product will be a different size for the 100 mg and 200 mg tablet.

If you have any questions concerning this petition, please contact me at 336-708-2842.

Sincerely,

Kathleen G. Palma

Kathleen G. Palma, Ph.D.
Vice President of Research, Development and Regulatory

204 Muirs Chapel Road Suite 200 Greensboro, NC 27410 Phone 336.544.0320 Fax 336.544.0322

2013-6823
CP

FDA-2013-P-0996

SUITABILITY PETITION

Identification of Petitioner:

Piedmont Animal Health
204 Muirs Chapel Road
Suite 200
Greensboro, NC 27410

Citation:

Piedmont Animal Health submits this petition under section 512 (n) (3) of the Federal Food, Drug, and Cosmetic Act.

Action Requested:

Piedmont Animal Health (PAH) requests permission from the Director to file an Abbreviated New Animal Drug Application (ANADA) for a different dosage form than the pioneer product.

Pioneer Product: SIMPLICEF™ Tablets (cefpodoxime proxetil)
Company: PHARMACIA & UPJOHN COMPANY
Division of Pfizer Inc. (Zoetis)
NADA #: 141-232
Active Ingredient: cefpodoxime
Species: canine

The pioneer product is a scored tablet formulation. It is a film-coated tablet. The proposed generic product will be a formed chewable tablet with a texture similar to semi-moist dog food. The amount of active ingredient will be the same for both pioneer and generic tablets. The method of administration (oral) will be the same for the proposed generic product as the parent product. A copy of pioneer labeling is enclosed.

Statement of Grounds:

The active ingredient in SIMPLICEF ™ is cefpodoxime formulated with cefpodoxime proxetil (prodrug) as a film-coated tablet. The pioneer product is administered orally in dogs for the treatment of skin infections (wounds and abscesses) in dogs caused by susceptible strains of *Staphylococcus intermedius, Staphylococcus aureaus, Streptococcus canis* (group G,*β hemolytic), Escherichia coli, Pasteurella multocida,* and *Proteus mirabilis*. The proposed generic product will have the same indications and dosage, be administered orally, have the same therapeutic effect and contain the same cautions and warnings as the pioneer product. The generic

will differ in two ways: the formulation of a film-coated tablet for the pioneer as compared to a formed soft chewable tablet for the generic product and the pioneer product is an elliptical, scored tablet while the generic product is a round, scored soft chewable tablet. The label will differ as it relates to the different companies manufacturing the two products, the trade name, the texture and hardness of the two products. The pioneer product states it is a film-coated tablet and the generic product will state it is a soft chewable tablet. The parts of the pioneer label that will be different are underlined. The underlined label is attached.

Environmental Impact:

In accordance with 21 CFR 25.15, Piedmont Animal Health claims that the agency requested action in this suitability petition qualifies for categorical exclusion from the requirement to prepare an environmental assessment as set forth in 21 CFR 25.30 (h). We confirm that to our knowledge no extraordinary circumstances exist that may significantly affect the quality of the human environment as described in 21 CFR 25.21.

Economic Impact:

Piedmont Animal Health will provide an economic impact analysis if requested by the Division.

Certification:

Attached is a statement that Piedmont Animal Health has included all known unfavorable information regarding this Suitability Petition.

Sincerely,

Kathleen G. Palma, Ph.D.
Vice President of Research and Development, Regulatory
Piedmont Animal Health

CERTIFICATION

The undersigned certifies that no unfavorable information related to this petition has been withheld from the attached Suitability Petition.

Kathleen G. Palma, Ph.D.

12 Aug 2013
Date

Address: Piedmont Animal Health
204 Muirs Chapel Road
Suite 200
Greensboro, NC 27410

LABELING

Attached is the pioneer labeling for SIMPLICEF™ (cefpodoxime proxetil). The label for Piedmont Animal Health will require revisions which are indicated by the underlined portion on the pioneer label.

SIMPLICEF

(cefpodoxime proxetil)

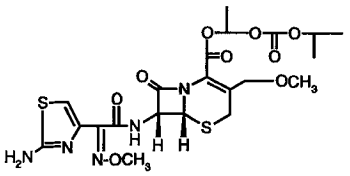
For oral use in dogs only

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

Cefpodoxime proxetil is an orally administered, extended spectrum, semi-synthetic cephalosporin antibiotic. The chemical name is: (+/-)-1-Hydroxyethyl(+)-(6R,7R)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-3-methoxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylate, 7$_Z$-(O-methyloxime), isopropyl carbonate (ester) [87239-81-4].

Cefpodoxime proxetil Chemical Structure:



Cefpodoxime proxetil is a prodrug; its active metabolite is cefpodoxime. All doses of SIMPLICEF (cefpodoxime proxetil) tablets are expressed in terms of the active cefpodoxime moiety. SIMPLICEF is available as:

100 mg Tablet, each reddish-orange, elliptical, scored tablet contains cefpodoxime proxetil equivalent to 100 mg of cefpodoxime.

200 mg Tablet, each light orange, round rectangle, scored tablet contains cefpodoxime proxetil equivalent to 200 mg of cefpodoxime.

INDICATION

SIMPLICEF tablets are indicated for the treatment of skin infections (wounds and abscesses) in dogs caused by susceptible strains of *Staphylococcus intermedius, Staphylococcus aureus, Streptococcus canis* (group G, ß-hemolytic), *Escherichia coli, Pasteurella multocida,* and *Proteus mirabilis.*

DOSAGE AND ADMINISTRATION

Dose range: The dose range of SIMPLICEF (cefpodoxime proxetil) tablets is 5-10 mg/kg (2.3-4.5 mg/lb) body weight, administered orally, once a day. The dose may be given with or without food. The determination of dosage for any particular patient must take into consideration such factors as the severity and nature of the infection, the susceptibility of the causative organisms, and the integrity of the patient's host-defense mechanisms. Obtain a sample of the pathogenic organism for culture and sensitivity testing prior to beginning antimicrobial therapy. Once results become available, continue with appropriate therapy.

Duration: SIMPLICEF tablets should be administered once daily for 5-7 days or for 2-3 days beyond the cessation of clinical signs, up to a maximum of 28 days. Treatment of acute infections should not be continued for more than 3-4 days if no response to therapy is seen.

Dosing Charts: For daily oral administration of SIMPLICEF at 5 mg/kg (Table 1) and 10 mg/kg (Table 2).

Table 1. Dose Table for SIMPLICEF Tablets at 5 mg/kg Total Daily Dosage

Weight of Dog (lb)						
Daily Dose		22	44	66	88	132
No. of 100 mg tablets		0.5	1	1.5		1
No. of 200 mg tablets					1	1
Weight of Dog (kg)						
Daily Dose		10	20	30	40	60
No. of 100 mg tablets		0.5	1	1.5		1
No. of 200 mg tablets					1	1

Table 2. Dose Table for SIMPLICEF Tablets at 10 mg/kg Total Daily Dosage

Weight of Dog (lb)						
Daily Dose	11	22	44	66	88	132
No. of 100 mg tablets	0.5	1		1		
No. of 200 mg tablets			1	1	2	3
Weight of Dog (kg)						
Daily Dose	5	10	20	30	40	60
No. of 100 mg tablets	0.5	1		1		
No. of 200 mg tablets			1	1	2	3

CONTRAINDICATIONS Cefpodoxime proxetil is contraindicated in dogs with known allergy to cefpodoxime or to the ß-lactam (penicillins and cephalosporins) group of antibiotics.

WARNINGS

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

PRECAUTIONS

The safety of cefpodoxime proxetil in dogs used for breeding, pregnant dogs, or lactating bitches has not been demonstrated. As with other cephalosporins, cefpodoxime proxetil may occasionally induce a positive direct Coombs' test.

ADVERSE REACTIONS

A total of 216 dogs of various breeds and ages ranging from 2 months to 15 years were included in the field study safety analysis. The following table shows the number of dogs displaying each clinical observation.

Table 3. Abnormal Health Findings in the U.S. Field Study[1]

Clinical Observation	SIMPLICEF (n=118)	Active Control (n=98)
Vomiting	2	4
Diarrhea	1	1
Increased water drinking	0	2
Decreased appetite	1	1

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

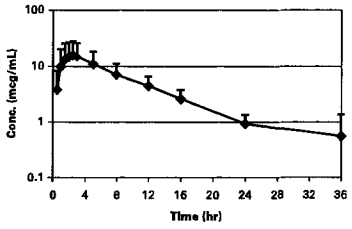
To report a suspected adverse reaction call 1-800-366-5288.

To request a material safety data sheet (MSDS) for SIMPLICEF tablets, call 1-800-733-5500.

CLINICAL PHARMACOLOGY

Pharmacokinetics/Pharmacodynamics: Cefpodoxime proxetil is a prodrug that is absorbed from and de-esterified in the gastrointestinal tract to its active metabolite, cefpodoxime. Following oral administration to fasting Beagles, oral bioavailability was 63.1 ± 5.3%.

Figure 1. Canine Plasma Concentration of Cefpodoxime After a Single Oral Dose of 10 mg/kg Cefpodoxime Proxetil Tablets



Cefpodoxime is distributed in the body with an apparent volume of distribution of 151 ± 27 mL/kg. Like other ß-lactam antibiotics, cefpodoxime is eliminated from the body primarily in the urine, with an apparent elimination half-life of approximately 5-6 hours after oral administration. This is similar to the 4.7 hour apparent elimination half-life observed after intravenous dosing. Following intravenous administration of 10 mg/kg, the average total body clearance (Cl_B) was 22.7 ± 4.19 mL/hr/kg.

Table 4. Summary of Pharmacokinetic Parameters Obtained after a Single Oral Dose of 10 mg Cefpodoxime/kg BW, Administered as a Tablet

PK Parameter	Unit	Tablet (SD)
$AUC_{0-\infty}$	mcg•hr/mL	145 (77.6)
AUC_{0-LOQ}	mcg•hr/mL	142 (77.5)
Maximum concentration (C_{max})	mcg/mL	16.4 (11.8)
Terminal plasma elimination half-life ($t_{1/2z}$)	hr	5.61 (1.15)
Time of maximum concentration (t_{max})	hr	2.21 (0.542)
Mean residence time ($MRT_{0-\infty}$)	hr	9.21 (1.97)

Microbiology: Like other ß-lactam antibiotics, cefpodoxime 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/or carboxypeptidase), which are essential for synthesis of the bacterial cell wall. Therefore, cefpodoxime is bactericidal. Cefpodoxime is stable in the presence of many common ß-lactamase enzymes. As a result, many organisms resistant to other ß-lactam antibiotics (penicillins and some cephalosporins) due to the production of ß-lactamases may be susceptible to cefpodoxime.

Cefpodoxime has a broad spectrum of clinically useful antibacterial activity that includes staphylococci, streptococci, and Gram-negative species (including *Pasteurella, Escherichia,* and *Proteus*). The compound is not active against most obligate anaerobes, *Pseudomonas* spp., or enterococci. The minimum inhibitory concentrations (MICs) for cefpodoxime against Gram-positive and Gram-negative pathogens isolated from canine skin infections (wounds and abscesses) in a 2002 U.S. field study are presented in Table 5. All MICs were determined in accordance with the National Committee for Clinical Laboratory Standards (NCCLS). Appropriate quality control (QC) ranges for *in vitro* susceptibility testing are presented in Table 6.

Table 5. Cefpodoxime Minimum Inhibitory Concentration Values (mcg/mL) from a 2002 Field Study Evaluating Skin Infections (wounds and abscesses) of Canines in the United States

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

† No Range, all isolates yielded the same value.

* Veterinary specific interpretive criteria have not been established for the above listed canine pathogens by the NCCLS at this time.

Table 6. Acceptable Quality Control Ranges for Cefpodoxime

	KB Disk Diffusion Method		Broth Micro-dilation Method
QC ATCC strain	Drug Concentration	Zone Diameter	MIC
Escherichia coli 25922	10 mcg	23-28 mm[a]	0.25-1 mcg/mL[a]
Staphylococcus aureus 25923	10 mcg	19-25 mm[a]	
Staphylococcus aureus 29213			1-8 mcg/mL[a]
Streptococcus pneumoniae 49619	10 mcg	28-34 mm[b]	0.03-0.12 mcg/mL[b]

[a] These ranges are for quality control strains used to monitor accuracy of minimum inhibitory concentrations (MICs) of non-fastidious organisms using cation-adjusted Mueller-Hinton agar or broth medium. The dilution range should encompass the QC ranges of these strains in the broth micro-dilution method.

[b] These ranges are for quality control strains used to monitor accuracy of minimum inhibitory concentrations (MICs) of fastidious organisms. When susceptibility testing is performed for *Streptococcus canis* (group G, ß-hemolytic), *Streptococcus pneumoniae* ATCC 49619 should be included as a QC strain in the presence of 5% lysed sheep blood (KB disk diffusion method) or 2.5% lysed horse blood (broth micro-dilution method).

EFFECTIVENESS

The clinical effectiveness of SIMPLICEF (cefpodoxime proxetil) was established in a multi-location (23 site) field study. In this study, 216 dogs with infected wounds or abscesses were treated with either SIMPLICEF (n=118) once daily at 5 mg/kg (2.3 mg/lb) body weight or with an active control antibiotic (n=98) administered twice daily for 5-7 days. In this study, SIMPLICEF was considered noninferior to the active control (88.7% versus 88.4% respectfully) in the treatment of canine skin infections (wounds and abscesses) caused by susceptible strains of *Staphylococcus intermedius, Staphylococcus aureus, Streptococcus canis* (group G, ß-hemolytic), *Escherichia coli, Pasteurella multocida,* and *Proteus mirabilis.*

ANIMAL SAFETY

In target animal safety studies, cefpodoxime was well tolerated at exaggerated daily oral doses of 100 mg/kg/day (10 times the maximum label dose) for 13 weeks in adult dogs and for 28 days in puppies (18-23 days of age). Therefore, once-daily administration of cefpodoxime oral tablets at the maximum labeled dose of 10 mg/kg for up to 28 days was shown to be safe in adult dogs and puppies.

Blood dyscrasia including neutropenias, may be seen following high doses of cephalosporins. Cephalosporin administration should be discontinued in such cases.

STORAGE INFORMATION

Store tablets at controlled room temperature 20° to 25°C (68° to 77°F). Replace cap securely after each opening.

HOW SUPPLIED

SIMPLICEF tablets are available in the following strengths (cefpodoxime equivalent), colors, and sizes:

100 mg (reddish-orange, elliptical, scored, debossed with 5226).....Bottles of 100

.....Bottles of 250

200 mg (light orange, round rectangle, scored, debossed with 5229).....Bottles of 100

.....Bottles of 250

NADA #141-232, Approved by FDA

Pfizer

Distributed by:
Pharmacia & Upjohn Company
Division of Pfizer Inc.
New York, NY 10017
Made in Belgium

REVISED LABELING FOR THE PIEDMONT ANIMAL HEALTH PRODUCT

The trade name of the product and the company manufacturing the product will be different and everywhere on the label that states the words "tablet" will be inserted to read "soft chewable tablet". The pioneer product is an elliptical, scored tablet (100 mg) and round rectangle, scored tablet (200 mg) while the generic product is a round soft chewable, scored tablet in different sizes to differentiate between the 100 and 200 mg tablets.

Other than the previously mentioned changes, the labeling of the generic product will be unchanged from the pioneer.

UPS Internet Shipping: View/Print Label

1. **Ensure there are no other shipping or tracking labels attached to your package.** Select the Print button on the print dialog box that appears. Note: If your browser does not support this function select Print from the File menu to print the label.

2. **Fold the printed sheet containing the label at the line so that the entire shipping label is visible. Place the label on a single side of the package and cover it completely with clear plastic shipping tape. Do not cover any seams or closures on the package with the label.** Place the label in a UPS Shipping Pouch. If you do not have a pouch, affix the folded label using clear plastic shipping tape over the entire label.

3. **GETTING YOUR SHIPMENT TO UPS**
   UPS locations include the UPS Store®, UPS drop boxes, UPS customer centers, authorized retail outlets and UPS drivers.
   Schedule a same day or future day Pickup to have a UPS driver pickup all of your Internet Shipping packages.
   Hand the package to any UPS driver in your area.
   Take your package to any location of The UPS Store®, UPS Drop Box, UPS Customer Center, UPS Alliances (Office Depot® or Staples®) or Authorized Shipping Outlet near you. Items sent via UPS Return Services(SM) (including via Ground) are also accepted at Drop Boxes. To find the location nearest you, please visit the 'Find Locations' Quick link at ups.com.

   Customers with a Daily Pickup
   Your driver will pickup your shipment(s) as usual.

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