Date of Approval: August 15, 2008

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-209

EXCEDE Sterile Suspension

Ceftiofur crystalline free acid
Cattle (beef, non-lactating dairy, and lactating dairy)

For the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii* in beef, non-lactating dairy, and lactating dairy cattle.

Sponsored by:

Pharmacia & Upjohn Co.,
a Division of Pfizer, Inc.

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-209
B. Sponsor:	Pharmacia & Upjohn Co. a Division of Pfizer, Inc. 235 East 42d St. New York, NY 10017 Drug Labeler Code: 000009
C. Proprietary Name:	EXCEDE Sterile Suspension
D. Established Name:	Ceftiofur crystalline free acid
E. Pharmacological Category:	Antimicrobial
F. Dosage Form:	Sterile oil suspension for injection
G. Amount of Active Ingredient:	200 mg ceftiofur equivalents (CE) per mL
H. How Supplied:	100 mL vial
I. How Dispensed:	Rx
J. Dosage(s):	Single injection of 6.6 mg CE/kg (3.0 mg CE/lb) body weight (BW) (1.5 mL sterile suspension per 100 lb BW)
K. Route(s) of Administration:	For subcutaneous (SC) injection in the posterior aspect of the ear where it attaches to the head (base of the ear) in lactating dairy cattle. For SC injection in the middle third of the posterior aspect of the ear or in the base of the ear in beef and non-lactating dairy cattle.
L. Species/Class(es):	Cattle (beef, non-lactating dairy, and lactating dairy)
M. Indication(s):	EXCEDE Sterile Suspension is indicated for treatment of bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* in beef, non-

lactating dairy, and lactating dairy cattle.

EXCEDE Sterile Suspension is also indicated for the control of respiratory disease in beef and non-lactating dairy cattle which are at high risk of developing BRD associated with *M. haemolytica*, *P. multocida*, and *H. somni*.

EXCEDE Sterile Suspension is also indicated for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii* in beef, non-lactating dairy, and lactating dairy cattle.

N. Effect(s) of Supplement: This supplement provides for a new indication, treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii* in beef, non-lactating dairy, and lactating dairy cattle.

II. EFFECTIVENESS:

A. Dosage Characterization:

This supplemental approval does not change the previously approved dosage. The Freedom of Information (FOI) Summary for the original approval of NADA 141-209 dated September 5, 2003, contains dosage characterization information for cattle.

B. Substantial Evidence:

1. Dose Confirmation Study

a. Title: "Clinical Efficacy of Ceftiofur Crystalline Free Acid Sterile Suspension Against Naturally Occurring Bovine Interdigital Necrobacillosis." Study Number 1133C-60-05-505. December 2006 to September 2007.

b. Investigators and Study Locations:

The study was conducted at four dairy sites and two feedlot sites in the U.S. and Canada.

Table 1. Summary of investigators and study locations.

Investigator	Location (animal type)
Michael Bossom, DVM	Clinton, IA (dairy)
Kelly Lechtenberg, DVM, PhD	Pender, NE (feedlot)
Scott Tripp, DVM	Dayton, ID (dairy)
Paul Busman, DVM	Sparta, MI (dairy)
Michael Capel, DVM	Perry, NY (dairy)
Calvin Booker, DVM, MS	Nanton, AB, Canada (feedlot)

c. Study Design:

1) *Objective:* To evaluate the effectiveness of a single SC administration of EXCEDE Sterile Suspension (ceftiofur crystalline free acid sterile suspension, CCFA-SS) in the base of the ear at a dose of 6.6 mg CE/kg BW, compared with vehicle-treated controls, for the treatment of naturally occurring foot rot in beef and dairy cattle.

2) *Test Animals:* A total of 177 cattle (70 crossbred beef steers and heifers and 107 Holstein and Holstein-cross lactating dairy cattle) were enrolled across the six locations. Cattle ranged from 6 months to 9 years of age, and ranged in weight from 562 to 1,159 lbs (beef) and from 1,040 to 2,125 lbs (dairy) BW at enrollment. Enrolled animals had no history of foot rot in the 30 days prior to enrollment. Vaccination for *Fusobacterium necrophorum* was not permitted; otherwise, the typical vaccination program was followed at each location. No antimicrobials or anti-inflammatory agents (including in-feed antimicrobials) were administered for at least 14 days prior to enrollment.

3) *Experimental Design:* Cattle were evaluated daily as part of the normal herd health practice. Cattle identified as lame were presented as potential study candidates to be scored by study personnel. Study candidates with a lameness score of 2 or 3 and a swelling score of 2 or 3 and a lesion score of 2 or 3 (using the scoring scales described below) in one foot only (the "qualifying foot") for two consecutive days were enrolled in the study. Cattle were assigned to treatment group according to a generalized block design and treated on the day they met the enrollment criteria (Day 0). Personnel conducting the foot rot evaluations were masked to the treatment assignments.

4) *Treatment Groups:*

Table 2. Summary of treatment groups.

Treatment	Dosage	No. of animals	
		Beef	Dairy
vehicle (control)	0.015 mL/lb BW* SC (base of the ear), as a single injection on Day 0	35	54
CCFA-SS	6.6 mg CE/kg BW SC (base of the ear), as a single injection on Day 0	35	53

*volume equivalent to CCFA-SS administered at 6.6 mg CE/kg BW

5) *Test Article Administration:* The test article was EXCEDE (CCFA-SS) Sterile Suspension, 200 mg CE/mL, with Miglyol® 812 and cottonseed oil (commercial formulation). The control article was CCFA-SS vehicle (the same formulation as the test article, without the active ingredient), as a sterile injectable solution. Test and control articles were administered by SC injection in the base of the ear once on the day of enrollment.

6) *Measurements and Observations:* Clinical signs of foot rot (lameness, swelling, and lesions) were recorded for all four feet of each animal at enrollment (Day 0). At enrollment, samples were collected from the affected interdigital lesions by swab and needle biopsy. General health observations were conducted from Day 1 to Day 7. Lameness scores were recorded for all four feet of each animal on Days 2, 4, and 7 post-treatment. Swelling and lesion scores were recorded for all four feet on Day 7 post-treatment.

The following scoring scales were used:

Lameness Scores: 0 = no lameness noted; 1 = favors foot, but moves readily; 2 = puts minimal weight on foot and moves slowly; 3 = holds foot up, reluctant to put weight on foot or move.

Swelling Scores: 0 = none, no swelling observed; 1 = slight, swelling observed only in the interdigital space; 2 = moderate, swelling involving the interdigital space and swelling extending into the soft tissue below the dewclaws; 3 = severe, swelling observed in the interdigital space and around the dewclaws; coronary band on one or both toes is red and swollen; ascending swelling and cellulitis may extend above the dewclaws.

Lesion Scores: 0 = no lesion; 1 = lesion healed or healing; 2 = small (≤ ¼ the length of the interdigital space) necrotic lesion; 3 = medium

(¼ to ¾ the length of the interdigital space) necrotic lesion; 4 = large (≥ ¾ the length of the interdigital space) necrotic lesion.

d. Statistical Analysis: The primary variable was treatment success rate. The individual animal was the experimental unit. A treatment success was defined as an animal that had a reduction from Day 0 to Day 7 of two or more scores in lameness (i.e., 3 to 1, 3 to 0, or 2 to 0), and a swelling score of 0 or 1 on Day 7, and a lesion score of 0 or 1 on Day 7 in the qualifying foot. If an animal developed lameness, lesions, or swelling due to bovine foot rot in any non-qualifying foot during the study, that foot had to score "0" for lameness, lesions, and swelling on Day 7 for the animal to be classified as a treatment success.

For statistical analyses, each animal was assigned a value of "0" (failure) or "1" (success). Success was analyzed using a generalized linear mixed model (GLMM); the macro GLIMMIX in SAS was utilized with a binomial error and logit link. The model included the fixed effects of treatment, type (beef and dairy), and treatment by type interaction; the random effects included site within type, treatment by site within type interaction, and residual. A 5% level of significance ($p \leq 0.05$) was used to assess statistical differences.

e. Results: Eight cattle were removed from the analysis due to protocol deviations or development of concurrent disease requiring treatment. A total of 169 cattle from six sites were included in the analysis.

The percentage of animals classified as a treatment success was significantly higher ($p = 0.0054$) in the CCFA-SS-treated group (45/84, 58.4%) compared to the control group (13/85, 13.2%). Treatment by type interaction was not significant, indicating that treatment was effective in both beef and dairy cattle.

f. Adverse Reactions: No test article-related adverse reactions were observed during the study.

g. Conclusion: The results of this study indicate that EXCEDE (CCFA-SS) Sterile Suspension, administered as a single SC dose of 6.6 mg CE/kg BW, is effective for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii*.

2. Identification of Bacterial Isolates and Determination of Mean Inhibitory Concentrations (MICs)

a. Title: "Presumptive and Final Identification of Isolates and the Minimum Inhibitory Concentration (MIC) Determinations for Anaerobic Bacteria Isolated from Clinical Cases of Bovine Foot Rot." Study Number 1176R-60-07-485. October 2007 to November 2007.

b. Methods: Foot rot pathogens were cultured from swabs and biopsy samples from animals enrolled in the pivotal effectiveness study (Study 1133C-60-05-505). Classical biochemical methods were used to definitively identify isolates of *F. necrophorum*. Classical biochemical methods were used to presumptively identify isolates as either *Prevotella* or *Porphyromonas* spp. with definitive identification based on the 16S ribosomal RNA gene sequence compared against the Ribosomal Database Project (RDP) database. Identification to the species level was confirmed if the gene sequence had ≥ 99% identity with gene sequences of previously defined species listed in the RDP database.

Ceftiofur MICs for *F. necrophorum* and *P. levii* were determined using the reference agar dilution method described by the Clinical and Laboratory Standards Institute (CLSI) document M11-A6.

c. Results: A total of 148 isolates were identified as *F. necrophorum* and 141 isolates were identified as *P. levii*. The MIC_{50}, MIC_{90}, and MIC range for each indicated pathogen are shown in Table 3. Ceftiofur demonstrated *in vitro* activity against both of the bacterial species that were isolated from cattle with clinical signs of bovine foot rot enrolled in the pivotal effectiveness study.

Table 3. Ceftiofur MIC values* of indicated pathogens isolated from cattle with naturally occurring bovine foot rot.

Indicated pathogens	Year of isolation	Number of isolates	MIC_{50}** (µg/mL)	MIC_{90}** (µg/mL)	MIC range (µg/mL)
Fusobacterium necrophorum	2006 to 2007	148	≤ 0.25	0.5	≤ 0.25 to >128
Porphyromonas levii	2006 to 2007	141	≤ 0.25	2.0	≤ 0.25 to 16

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

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 141-209 dated September 5, 2003, and for the supplemental approval of NADA 141-209 dated June 2, 2006, contain summaries of target animal safety studies for beef, non-lactating, and lactating dairy cattle.

IV. HUMAN FOOD SAFETY:

A. Toxicology:

CVM did not require toxicology studies for this supplemental approval. The FOI Summaries for the original approval of NADA 140-338 (NAXCEL Sterile Powder) dated January 25, 1988; for the supplemental approval of NADA 140-338 dated May 21, 1996; for the original approval of NADA 140-890 (EXCENEL RTU Sterile Suspension) dated April 1996; and for the original approval of NADA 141-235 (EXCEDE for Swine) dated June 18, 2004, contain summaries of all toxicology studies for ceftiofur.

B. Residue Chemistry:

1. Summary of Residue Chemistry Studies

CVM did not require residue chemistry studies for this supplemental approval. The total residue depletion and metabolism in the target species and comparative metabolism in the toxicological species for ceftiofur are summarized in the FOI Summaries cited above for NADA 140-338 and NADA 140-890. The FOI Summary for the original approval of NADA 141-209 dated September 5, 2003, and for the supplemental approval of NADA 141-209 dated June 2, 2006, contain summaries of residue chemistry studies for ceftiofur crystalline free acid in beef, non-lactating, and lactating dairy cattle.

2. Target Tissue and Marker Residue Assignment

The target tissue for residue monitoring is kidney. The marker residue in edible tissues, including milk, is the sum of ceftiofur and desfuroylceftiofur-related metabolites, measured by high performance liquid chromatography (HPLC) as the stable derivative desfuroylceftiofur acetamide (DCA).

3. Tolerance Assignments

Cattle tolerances are 0.4 ppm DCA in kidney, 2 ppm DCA in liver, 1 ppm DCA in muscle, and 0.1 ppm DCA in milk. For research purposes, a value of 95 ppm DCA has been established for making decisions regarding the safety of residues at the injection site. See the FOI Summary for the supplemental approval of NADA 141-209 dated June 2, 2006.

4. Withdrawal and Milk Discard Times

A 13-day pre-slaughter withdrawal period is assigned for EXCEDE Sterile Suspension when this product is used according to label directions in beef, non-lactating, and lactating dairy cattle. No milk discard time is required when this product is used according to label directions. See the FOI Summary for the supplemental approval of NADA 141-209 dated June 2, 2006.

C. Microbial Food Safety:

The Agency evaluated a microbial food safety risk assessment for the use of ceftiofur crystalline free acid for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii* in beef, non-lactating dairy, and lactating dairy cattle. In beef and non-lactating dairy cattle, the product is administered as a SC injection either in the middle third of the posterior aspect of the ear or in the dorsal posterior aspect of the ear where it attaches to the head (base of the ear) at a dosage of 3.0 mg CE/lb (6.6 mg CE/kg) BW (1.5 mL sterile suspension per 100 lb BW). In lactating dairy cattle, the product is administered as a SC injection in the base of the ear at a dosage of 3.0 mg CE/lb (6.6 mg CE/kg) BW (1.5 mL sterile suspension per 100 lb BW).

The risk assessment involved conducting: 1) a *release assessment* to describe the probability that the antimicrobial new animal drug and its use in animals will result in the emergence of resistant bacteria or resistance determinants in the food animal under proposed conditions of use; 2) an *exposure assessment* to describe the likelihood of human exposure to the resistant bacteria or resistance determinants through consumption of edible products from treated animals; and 3) a *consequence assessment* to describe the potential human health consequences of exposure to the defined resistant bacteria or resistance determinants by considering the human medical importance of third generation cephalosporins in the treatment of human infectious disease.

It was determined that there is high risk associated with this use of ceftiofur crystalline free acid. Risk mitigation strategies, such as prescription only (Rx) marketing status, injectable administration in individual animals, and continued monitoring in the National Antimicrobial Resistance Monitoring System (NARMS), are appropriate for managing the overall risk estimation of high associated with this use of ceftiofur crystalline free acid for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii* in beef, non-lactating and lactating dairy cattle.

D. Analytical Method for Residues:

The regulatory method for determination of DCA in bovine kidney, muscle, and milk is the HPLC-DCA assay which successfully completed a sponsor-monitored multi-laboratory method trial. The method is on file with the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

V. USER SAFETY:

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

FOR USE IN ANIMALS ONLY. NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.

Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposures to such antimicrobials, including ceftiofur, may elicit mild to severe allergic reactions in some individuals. Repeated or prolonged exposure may lead to sensitization. Avoid direct contact of the product with the skin, eyes, mouth and clothing. Sensitization of the skin may be avoided by wearing latex gloves.

Persons with a known hypersensitivity to penicillin or cephalosporins should avoid exposure to this product.

In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g., skin rash, hives, difficult breathing), seek medical attention.

The material safety data sheet contains more detailed occupational safety information. To obtain a material safety data sheet please call 1-800-733-5500. To report any adverse event please call 1-800-366-5288.

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 EXCEDE Sterile Suspension, when used according to the label, is safe and effective for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii* in beef, non-lactating dairy, and lactating dairy cattle. Additionally, data demonstrate that residues in food products derived from cattle treated with EXCEDE Sterile Suspension will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

Labeling restricts this drug to use by or on the order of a licensed veterinarian. This decision was based on the following factors: (a) adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this product to treat bovine foot rot and (b) restricting this drug to use by or on the order of a licensed veterinarian should help prevent indiscriminate use which could result in violative tissue residues.

B. Exclusivity:

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The three years of marketing exclusivity apply only to the bovine foot rot indication for which this supplement is approved.

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)(2)).

D. Patent Information:

EXCEDE Sterile Suspension is under the following U.S. patent number:

U.S. Patent Number	Date of Expiration
5,721,359	February 24, 2015

VII. ATTACHMENTS:

Facsimile Labeling:

A. EXCEDE Sterile Suspension - Vial Label
B. EXCEDE Sterile Suspension - Package Insert
C. EXCEDE Sterile Suspension – Carton