Date of Approval: September 15, 2010

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-235

EXCEDE for Swine

Ceftiofur Crystalline Free Acid
Sterile Suspension
Swine

For the control of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Haemophilus parasuis*, and *Streptococcus suis* in groups of pigs where SRD has been diagnosed.

Sponsored by:

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

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-235
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 for Swine
D. Established Name:	Ceftiofur crystalline free acid (CCFA)
E. Pharmacological Category:	Antimicrobial
F. Dosage Form:	Sterile oil suspension for injection
G. Amount of Active Ingredient:	100 mg ceftiofur equivalents (CE) per mL
H. How Supplied:	100 mL glass vial
I. How Dispensed:	Rx
J. Dosage:	Single injection of 5.0 mg CE/kg (2.27 mg CE/lb) body weight (1.0 mL sterile suspension per 44 lb body weight). No more than 2 mL should be injected in a single injection site.
K. Route of Administration:	Intramuscular (IM) injection in the post-auricular region of the neck
L. Species/Class:	Swine
M. Indications:	EXCEDE For Swine Sterile Suspension 100 mg/mL is indicated for the treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Haemophilus parasuis*, and *Streptococcus suis*; and for the control of SRD associated with *A. pleuropneumoniae*, *P. multocida*, *H. parasuis*, and *S. suis* in groups of pigs where SRD has been diagnosed.
N. Effect of Supplement:	This supplement provides for a new indication for the control of SRD associated with

A. pleuropneumoniae, *P. multocida*, *H. parasuis*, and *S. suis* in groups of pigs where SRD has been diagnosed.

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 141-235 dated June 18, 2004, contains dosage characterization information for swine.

B. Substantial Evidence:

The effectiveness of EXCEDE for Swine (ceftiofur crystalline free acid, CCFA) sterile suspension for the treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Haemophilus parasuis*, and *Streptococcus suis* was demonstrated in the original approval of NADA 141-235 and is summarized in the FOI Summary dated June 18, 2004.

A multi-site natural infection field study (dose confirmation study) was conducted to confirm the effectiveness of EXCEDE for Swine for the control of SRD in groups of pigs where SRD has been diagnosed.

Dose Confirmation Study

1. Title: "Evaluation of EXCEDE for Swine for the Control of Swine Respiratory Disease." Study Number 1123C-60-08-315. January 2009 to April 2009.

2. Investigators:

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   Paul Yeske, DVM; Swine Veterinary Center, St. Peter, MN
   Martin Mohr, DVM; New Ulm Regional Veterinary Center, New Ulm, MN

3. Study Design:

   a. *Objective:* To evaluate the effectiveness of EXCEDE for Swine (CCFA) sterile suspension for the control of SRD in groups of pigs where SRD has been diagnosed.

b. *Test Animals:* A total of 762 commercial feeder pigs (female and castrated male) were enrolled across 10 study sites. Pigs ranged from 4 to 19 weeks of age, and weighed 8 to 122 lbs at enrollment. Each investigator purchased study candidates from commercial swine operations that had previously experienced an SRD outbreak and transported them to the study site. Each site enrolled two pens of pigs (33 to 40 pigs per pen).

c. *Test Article Administration:* The test article was EXCEDE for Swine (CCFA) sterile suspension, 100 mg ceftiofur equivalents (CE)/mL (commercial formulation). The control article was 0.9% sterile saline injectable solution. Treatments were administered by intramuscular (IM) injection in the lateral neck. The following table summarizes the treatment groups.

Table 1. Summary of treatment groups.

Group	Treatment Regimen	No. of Animals
T01	saline; 1 mL/44 lb body weight (BW)* IM as a single injection on Day 0	383
T02	CCFA; 2.27 mg CE/lb (5 mg/kg) BW IM as a single injection on Day 0	379

*volume equivalent to CCFA administered at 2.27 mg CE/lb BW

d. *Measurements and Observations:* Study candidates were evaluated daily for clinical signs of SRD. An outbreak of SRD was defined as the day (Day 0) when at least 15% of study candidates in a pen had a respiratory score ≥ 2 (on a scale of 0 to 3 where 0 is normal), and a depression score ≥ 2 (on a scale of 0 to 3 where 0 is normal), and a rectal temperature of ≥ 104 °F. The first pig in a pen meeting the SRD criteria was euthanized and necropsied to characterize the disease outbreak; euthanized animals did not count towards the 15% needed to initiate treatment. When the pen met the 15% outbreak threshold, the remaining pigs in the pen were assigned to treatment groups and treated with CCFA or saline.

General health observations were conducted once daily until enrollment was complete, twice daily from Day 0 through Day 6, and once on Day 7. All pigs remaining in the pen on Day 7 were clinically evaluated for respiratory score, depression score, and rectal temperature, and then were euthanized and necropsied. A pig was classified as a treatment success on Day 7 if it was alive and had a respiratory score ≤ 1, and a depression score ≤ 1, and a rectal temperature of < 104 °F. Pigs that were not classified as treatment successes were classified as treatment failures.

At necropsy, the percentage of pneumonic lung lesions was estimated and a weighted lung lesion score was determined using the following ratios of individual lung lobes to total lung mass: left cranial 10%, left middle 10%,

left caudal 25%, right cranial 10%, right middle 10%, right caudal 25%, and accessory 10%. Lung tissue, lung swab, and pleural swab samples were collected from non-treated pigs euthanized prior to enrollment and from saline- and CCFA-treated pigs that died or were euthanized during the study.

The individuals performing clinical assessments and necropsies were masked to treatment and did not participate in treatment administration.

4. Statistical Analysis: The individual animal was the experimental unit. Pigs were assigned to treatment based on a randomized complete block design. Treatment groups were commingled in pens.

   The primary variable for evaluating effectiveness was treatment success rate. Lung lesion percentage and mortality were evaluated as secondary variables. Treatment success rate was analyzed using a generalized linear mixed model (GLIMMIX) in SAS. The model included the fixed effect of treatment and the random effects of site, site by treatment, block within site and pen, pen within site, and residual. Back-transformed least squares means were estimated and 95% confidence intervals were reported. A one-sided 5% level of significance ($p \leq 0.05$) was used to assess statistical significance.

5. Results:

   A total of 693 enrolled pigs were included in the analysis. The remaining 69 enrolled pigs were removed from the study for non-SRD reasons, dosing errors, or significant protocol deviations and were excluded from the effectiveness analysis.

   a. *Treatment Success*: The back-transformed least squares mean percentage of pigs classified as treatment successes was statistically significantly higher ($p = 0.0188$) in the CCFA-treated group (198/346, 59.6%) compared to the control group (148/347, 41.4%).

   b. *Secondary Variables*: The total lung lesion percentage and the number of mortalities associated with SRD were lower in the CCFA-treated group compared to the control group.

   c. *Microbiology: A. pleuropneumoniae* (35 isolates), *P. multocida* (77 isolates), *H. parasuis* (92 isolates), and *S. suis* (195 isolates) were isolated in sufficient numbers from pleural swabs, lung swabs, and lung tissue from non-treated pigs euthanized prior to enrollment and from saline- and CCFA-treated pigs that died or were euthanized during the study. Isolates of *P. multocida* and *S. suis* were identified using a commercial identification system. Isolates of *A. pleuropneumoniae* and *H. parasuis* were identified by using species-specific polymerase chain reactions (PCR) methods.

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

7. Conclusion: Based on the results of this study, EXCEDE for Swine (CCFA) sterile suspension administered as a single IM dosage of 5 mg/kg (2.27 CE/lb) BW was effective for the control of SRD associated with *A. pleuropneumoniae*, *P. multocida*, *H. parasuis*, and *S. suis* in groups of pigs where SRD has been diagnosed.

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 141-235 dated June 18, 2004, contains a summary of target animal safety studies for swine.

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 dated January 25, 1988, NADA 140-890 dated April 26, 1996, and NADA 141-235 dated June 18, 2004, contain summaries of all toxicology studies for use in swine.

The potential for residues of CCFA to affect the human intestinal flora is addressed in the original approval for this NADA (approval date June 18, 2004). The Agency concluded that the amount of microbiologically active residues of CCFA that reach the colon would most likely not cause adverse effects on the human intestinal flora of the consumer.

B. Residue Chemistry:

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-235 dated June 18, 2004, contains a summary of residue chemistry studies for swine.

C. Microbial Food Safety:

The Agency carefully reviewed a microbial food safety risk assessment provided by the sponsor regarding the use of ceftiofur crystalline free acid as a single intramuscular injection at a dose of 5.0 mg ceftiofur equivalents/kg body weight in swine for control of SRD associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Haemophilus parasuis*, and *Streptococcus suis* in groups of swine where SRD has been diagnosed. The identified hazards are cephalosporin-resistant *Salmonella* and uropathogenic *Escherichia coli* resulting from this use of ceftiofur crystalline free acid that infect humans and are subsequently treated with a cephalosporin antibiotic.

The Agency's review concluded a *release assessment* outcome of HIGH, an *exposure assessment* outcome of MEDIUM for *Salmonella* and HIGH for *E. coli*, and a *consequence assessment* outcome of HIGH. Integration of these outcomes results in an overall risk categorization of this use of ceftiofur crystalline free acid as HIGH, appropriate for Category 1 risk management strategies.

The *release assessment* considered many things, including, but not limited to, the mode of action and spectrum of activity of the drug, the baseline prevalence of resistance, mechanisms of resistance, pharmacokinetics and pharmocodynamics of the drug, and possible selection pressure resulting from this use of ceftiofur crystalline free acid. The Agency considers the outcome of the *release assessment* to be HIGH because of the easily transmissible nature of the most common β-lactamases, the high background prevalence of resistance, and the selection pressure imposed by use of ceftiofur crystalline free acid in swine. The Agency considers the *exposure assessment* to be MEDIUM for *Salmonella* due to low rates of *Salmonella* contamination of pork products, combined with a high rate of consumption of pork. The uropathogenic *E. coli* (UPEC) contamination rate of pork products is considered MEDIUM, resulting in an overall *exposure assessment* of HIGH risk of human exposure to UPEC from consumption of pork. The outcome of the *consequence assessment* is HIGH, due to the critical importance of third-generation cephalosporins in human medicine.

Risk management considerations for this approval are all consistent with those outlined for a Category 1 drug, with the exception of a medium extent of use; however, evidence presented by the sponsor demonstrating current extra-label ceftiofur use for the control of swine respiratory disease supports allowance of a medium extent of use for this Category 1 drug. The Agency concludes that there should not be an increased risk to human health due to antimicrobial resistance issues associated with the new indication for ceftiofur crystalline free acid use in swine.

D. Analytical Method for Residues:

The FOI Summary for the original approval of NADA 141-235 dated June 18, 2004, contains the analytical method summaries for ceftiofur crystalline free acid in swine.

The validated regulatory methods for detection and confirmation of residues of ceftiofur crystalline free acid are available from CVM, FDA, 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 for Swine:

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 protective 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 report adverse effects in users, to obtain more information or to obtain a material safety data sheet, 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 for Swine, when used according to the label, is safe and effective for the control of SRD associated with *A. pleuropneumoniae*, *P. multocida*, *H. parasuis*, and *S. suis* in groups of pigs where SRD has been diagnosed. Additionally, data demonstrate that residues in food products derived from swine treated with EXCEDE for Swine 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 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 swine respiratory disease, and (b) restricting this drug to use by or on 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 applies only to the control of swine respiratory disease 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 for Swine is under the following U.S. patent numbers:

U.S. Patent Number	Date of Expiration
5,721,359	February 1, 2015

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

VII. ATTACHMENTS:

Facsimile labeling is attached as indicated below.

A. EXCEDE for Swine - Vial Label
B. EXCEDE for Swine - Package Insert
C. EXCEDE for Swine – Shipper Label