DATE OF APPROVAL LETTER: FEBRUARY 8, 2002

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 140-890

EXCENEL® RTU Sterile Suspension
A brand of ceftiofur hydrochloride sterile suspension

"For the treatment of acute metritis (0-14 days post-partum) in cattle"

SPONSORED BY:

PHARMACIA & UPJOHN

I. GENERAL INFORMATION

NADA Number:	140-890
Sponsor:	Pharmacia & Upjohn Company 7000 Portage Rd. Kalamazoo, MI 49001
Established Name:	ceftiofur hydrochloride
Proprietary Name:	EXCENEL® RTU Sterile Suspension
Marketing Status:	This is a prescription product and will include the caution statement as follows: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian
Effect of this Supplement:	This supplement provides a new indication, within the currently approved dose and duration, for use of ceftiofur hydrochloride sterile suspension (EXCENEL® RTU Sterile Suspension) in cattle, for the treatment of acute metritis (0-14 days post-partum) associated with bacterial organisms susceptible to ceftiofur.

II. INDICATIONS FOR USE

For the treatment of bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia* spp. (*Pasteurella haemolytica)*, *Pasteurella multocida* and *Haemophilus somnus*, for the treatment of acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*, and for the treatment of acute metritis (0-14 days post-partum) associated with bacterial organisms susceptible to ceftiofur.

III. DOSAGE

A. *Dosage Form:* Sterile Suspension available in 100 mL vials, each mL contains ceftiofur hydrochloride equivalent to 50 mg ceftiofur.

B. *Route of Administration:* Administered by either intramuscular or subcutaneous injection in cattle.

C. *Recommended dosage:* For acute metritis administer at a dose of 1.0 mg ceftiofur equivalents (CE)/lb (2.2 mg CE/Kg) body weight (BW), 2 mL/ 100 lb BW. Administer at 24-hour intervals for a total of five consecutive days.

IV. EFFECTIVENESS

Data from the following multi-location clinical effectiveness study demonstrate that EXCENEL® RTU Sterile Suspension is effective for the treatment of acute metritis (0 to 14 day post-partum) associated with bacterial organisms sensitive to ceftiofur.

1. Objective: To evaluate under clinical field conditions, effectiveness of ceftiofur hydrochloride sterile suspension administered parenterally at dosages of 0.5 or 1.0 mg CE/lb BW (1.1 or 2.2 mg CE/kg BW) for 5 consecutive days for the treatment of acute post-partum metritis in dairy cows. Ceftiofur hydrochloride is approved for the treatment of bovine respiratory disease and interdigital necrobacillosis (foot rot, pododermatitis) at these dosages.

2. Study Investigators:
Paul Busman, DVM, Coopersville, MI; Steve Carlson, DVM, Tulare, CA; Phillip Jardon, DVM, Visalia, CA; Alfred Harper, DVM, Dublin, TX; Art Sherman, DVM, Geneva, NY; Tony Wiseley, DVM, Perry, NY; Gerard Koenig, DVM, Corcoran, CA; Carlos Risco, DVM, Gainesville, FL.

3. General Design:

   a. Experimental animals: Lactating dairy cows (N = 406) at eight commercial dairies were enrolled that met the following criteria: less than 15 days post-partum, rectal temperature ≥ 103°F (39.5°C), a fetid vaginal/uterine discharge, and no clinical signs of other diseases of the respiratory or digestive tracts detected during a physical examination.

   b. Dosage form: Ceftiofur hydrochloride sterile suspension (50 mg CE/mL), a ready to use formulation (EXCENEL® RTU Sterile Suspension). The control animals were administered sterile saline.

   c. Experimental Design: As cows were found to be eligible for inclusion, they were randomly assigned in blocks to one of three groups: control (sterile saline for injection) or ceftiofur hydrochloride at 0.5 mg or 1.0 mg CE/lb BW (1.1 or 2.2 mg CE/kg BW). All treatments were administered by either subcutaneous or intramuscular injection for 5 consecutive days. Rectal temperature and vaginal discharge were evaluated 6, 10 and 14 days after the initial treatment. Cows that had not been administered additional antimicrobial therapy (escape therapy) and with rectal temperature less than 103°F (39.5°C) and without fetid discharge were defined as cured. Cows

administered additional antimicrobial therapy or with rectal temperature ≥ 103°F (39.5°C) or with a fetid discharge were defined as failed to cure.

d. Statistical Analyses: Of the 406 cows enrolled into the study 30 were removed completely from statistical analyses because they did not fulfill the study requirements (deviations to the protocol). Of the remaining 376 cows, 15 cows either had an observation missing or violated the protocol; therefore, there were 361 cows included in the analyses for cure rates on Day 14; 116, 124 and 121 animals in the saline, 0.5 mg, and 1.0 mg CE/lb BW treatment groups, respectively. The cure rates for each of the ceftiofur treatment groups were compared against the control using the generalized linear mixed model. Rectal temperatures were statistically analyzed at four time periods/points: over the first five days of the study (during treatment); on Day 6; on Day 10; and on Day 14.

5. Results: On Day 14 the 1.0 mg CE/lb BW treatment group had the highest cure rate (77%), followed by the 0.5 mg CE/lb BW treatment group, and the control group (65% and 62%, respectively). The cure rate for the 1.0 mg CE/lb BW treatment group was significantly higher than that of the control group on Day 14 (p=0.010). No difference was detected between the 0.5 mg CE/lb BW treatment group and the control group (p=0.295).

6. Conclusions: The results of this study demonstrate that ceftiofur hydrochloride administered daily for five consecutive days at a dose of 1.0 mg ceftiofur equivalents/lb BW (2.2 mg/kg BW) is an effective treatment for acute metritis (0-14 days post-partum) in cattle.

CLINICAL MICROBIOLOGICAL DATA:

A summary of updated MIC data for swine and cattle pathogens is presented in tabular format in the labeling for EXCENEL® RTU Sterile Suspension. This format is similar to that used for NAXCEL® Sterile Powder (See Supplemental Approval; NADA 140-338, dated July 6, 2000).

V. ANIMAL SAFETY

Ceftiofur hydrochloride sterile suspension was approved previously (NADA 140-890. April 26, 1996) for administration to cattle at dosages of 0.5 to 1.0 mg ceftiofur equivalents per pound body weight (1.1 to 2.2 mg CE/kg BW) for up to five consecutive days for the treatment of bacterial respiratory disease and acute interdigital necrobacillosis (foot rot). Because the dose used for acute post-partum metritis falls within the previously approved dosage regimen, data on file in NADA 140-890 provide sufficient evidence of animal safety for this dosing regimen. Therefore, no additional studies were required for this supplemental application.

VI. HUMAN SAFETY

Ceftiofur hydrochloride was approved previously (NADA 140-890, April 26, 1996) for administration to cattle, including dairy cows, at dosages of 0.5 to 1.0 mg ceftiofur equivalents per pound body weight (1.1 to 2.2 mg CE/kg BW) for up to five consecutive days for the treatment of bacterial respiratory disease and acute interdigital necrobacillosis (foot rot). Because the dose for treatment of acute post-partum metritis falls within the previously approved dosage regimen, data on file in NADA 140-890 provide sufficient evidence of human food safety for this dosing regimen. Therefore, no additional toxicology or residue studies were required for this supplemental application.

VIII. AGENCY CONCLUSIONS

The data submitted in support of this supplemental application satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations to enable FDA to revise 21 CFR 522.314 to provide for the safe and effective use of EXCENEL® RTU Sterile Suspension for the treatment of acute metritis (0-14 days post-partum) associated with bacterial organisms susceptible to ceftiofur in cattle.

The product remains a prescription drug for safe and effective use by or on the order of a licensed veterinarian.

In accordance with 21 CFR 514.106(b)(2)(v), this is a Category II change which did not require a reevaluation of the human food and target animal safety data in the parent application.

Under Section 512 (c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval for food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or, in the case of food producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of the supplement and conducted or sponsored by the applicant. The THREE years of marketing exclusivity applies only to the new indication for which the supplemental application is approved.

EXCENEL® RTU Sterile Suspension is under patent numbers U.S. 4,902,683 expiring February 20, 2007, and U.S. 5,736,151 expiring April 7, 2015.

IX. APPROVED PRODUCT LABELING

A copy of the facsimile labeling, including the package insert, is attached to this document.

Copies of applicable labeling may be obtained by writing to:

Freedom of Information Staff (HFI-35)
Food and Drug Administration, Room 12A16
5600 Fisher's Lane
Rockville, Maryland 20857