FREEDOM of INFORMATION SUMMARY

Supplement to NADA 140-338

NAXCEL® Sterile Powder
(ceftiofur sodium)

" for the treatment of bovine respiratory disease (BRD) associated with *Pasteurella haemolytica, Pasteurella. multocida* and *Haemophilus somnus,* and for the treatment of acute bovine interdigital necrobacillosis (foot rot) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*."

SPONSORED BY:

PHARMACIA & UPJOHN COMPANY

Date of Approval: May 29, 2001

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I. GENERAL INFORMATION

NADA Number: 140-338

Sponsor: Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001

Accepted Name: ceftiofur sodium sterile powder

Trade Name: NAXCEL® brand of ceftiofur sodium sterile powder.

Marketing Status: This is a prescription product which includes the caution statement as follows: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Supplement Effect: Provides for the use of a subcutaneous (SC) route of administration for NAXCEL® Sterile Powder in cattle.

II. INDICATIONS FOR USE

NAXCEL® Sterile Powder is indicated for the treatment of Bovine Respiratory Disease (BRD) associated with *Pasteurella multocida, Pasteurella haemolytica*, and *Haemophilus somnus* and for the treatment of acute bovine interdigital necrobacillosis (foot rot) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND DOSAGE

A. *Dosage Form:* NAXCEL® Sterile Powder is available in 1 g and 4 g vials. Following reconstitution, each mL contains ceftiofur sodium equivalent to 50 mg ceftiofur.

Unreconstituted NAXCEL® Sterile Powder should be stored at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Reconstituted NAXCEL® Sterile Powder should be stored either in a refrigerator 2° to 8°C (36° to 46°F) for up to 7 days or at controlled room temperature 20° to 25°C (68° to 77°F) [see USP] for up to 12 hours.

B. *Route of Administration:* NAXCEL® Sterile Powder should be administered by intramuscular (IM) or subcutaneous (SC) injection in cattle.

C. *Recommended Dosage:* NAXCEL® Sterile Solution is to be administered IM or SC to cattle at the dosage range of 0.5 to 1.0 mg ceftiofur per pound (lb) of body weight (BW); 1 to 2 mL reconstituted sterile solution per 100 lb BW. Treatment should be repeated every 24 hours for a total of three treatments. Additional treatments may be given on Days 4 and 5 to animals which do not show a satisfactory response (not recovered) after the first three treatments. Do not inject more than 15 mL per IM injection site.

Note: Following subcutaneous administration of ceftiofur sodium in the neck, small areas of discoloration at the site may persist beyond five days, potentially resulting in trim loss of edible tissues at slaughter.

As with any parenteral injection, localized post-injection bacterial infections may result in abscess formation. Attention to hygienic procedures can minimize their occurrence.

IV. EFFECTIVENESS

NAXCEL® Sterile Powder (ceftiofur sodium) is approved (0.5 to 1.0 mg ceftiofur/lb BW for 3 to 5 days, intramuscularly – NADA 140-338) for use in beef and lactating cattle for the treatment of bacterial respiratory disease associated with *Pasteurella haemolytica, Pasteurella multocida* and *Haemophilus somnus*. By this route of administration, no injection site blemishes are noted at the site of injection. However, because of the escalating concern in the beef cattle industry over intramuscular injection sites and the potential injection site blemishes that ensue in edible tissue, there is additional interest in NAXCEL® Sterile Powder for the treatment of bovine respiratory disease and foot rot using the SC route of administration. The following study was conducted to demonstrate the bioequivalence of ceftiofur sodium when administered IM or SC to cattle.

A. Bioequivalence Study - TR No. 788-7926-96-014

1. Title: Bioequivalence of ceftiofur sodium (NAXCEL® Sterile Powder) administered IM or SC to cattle.

2. Investigators: Scott A. Brown, S. Theodore Chester, Amanda K. Speedy, V. Larry Hubbard, J. Kenneth Callahan, Philip J. Hamlow, Beth Hibbard and Edward J. Robb. Pharmacia & Upjohn Company, Kalamazoo, MI 49001.

3. General Design:

   a. Purpose: Determine if bioequivalence exists between the 72-hour plasma disposition of ceftiofur and desfuroylceftiofur-related metabolites (measured as desfuroylceftiofur acetamide) by IM or SC at a dose of 2.2 mg ceftiofur free acid equivalents (CFAE)/kg.

   b. Experimental Animals: Twelve (12) crossbred beef cattle (6 males and 6 females) 224 to 254 kg BW at start of study.

   c. Dosage Form: NAXCEL® Sterile Powder, 2.2 mg ceftiofur free acid equivalents/kg (1.0 mg CE/lb) as ceftiofur sodium.

   d. Experimental Design: Cattle were included in a three-period, two-treatment crossover design (ABB/BAA). Treatment A used the SC route of administration, treatment B used the IM route of administration. There was a 14-day washout period between doses.

   e. Sampling: Blood samples were collected before dosing and at 20 and 40 minutes and 1, 1.5, 2, 3, 4, 8, 12, 16, 24, 36, 48, 60, 72, and 96 hours after treatment administration.

   f. Assay Method: HPLC of ceftiofur and desfuroylceftiofur-related metabolites. The Limit of Quantitation (LOQ) is 0.15 mg CE/mL plasma. Each sample was analyzed as a single determination.

   g. Pharmacokinetics Analysis Method – The main pharmacokinetic parameters were estimated using noncompartmental analysis. Area Under the Curve (AUC) values were calculated using the trapezoidal rule.

   h. Decision Criteria - A priori, the area under the curve from time zero to the limit of quantitation ($AUC_{0\text{-}LOQ}$), and the time concentrations which exceeded 0.2 μg/mL ($t_{>0.2}$) were used to establish equivalence. The 90% confidence interval for difference in the two routes of administration, for each parameter, was required to reside within ± 20% of the reference mean to conclude equivalence of the two routes of administration.

4. Results: Both decision criteria for acceptance of equivalence of ceftiofur sodium by the two routes of administration were satisfied ($AUC_{0\text{-}LOQ}$ and $t_{>0.2}$). Furthermore, the t-based 90% confidence interval for the observed maximum concentration meets the classic bioequivalence criteria of being totally contained within ± 20% of the reference mean. Therefore, the SC route of administration of ceftiofur sodium is considered to be bioequivalent to that of the IM route of administration of ceftiofur sodium. This conclusion leads to the

interpretation that the two routes of administration are interchangeable with respect to efficacy, systemic target animal safety, and human food safety (except for SC injection site blemishes) for ceftiofur sodium in cattle.

V. ANIMAL SAFETY

The safety of ceftiofur sodium has been demonstrated in studies discussed in the FOI summary for NAXCEL® Sterile Powder NADA 140-338.

In addition to the previous submission cited alone, injection sites were evaluated as part of a study conducted to evaluate the tissue (kidney, muscle and serum) levels of ceftiofur sodium (NAXCEL® Sterile Powder) administered by subcutaneous injection for 5 consecutive days (SR #a0058234).

A. Injection Site Safety: SR a0058234

Injection site and kidney residue evaluation and gross pathology after SC administration of ceftiofur sodium (NAXCEL® Sterile Powder) at a dose of 2.2 mg ceftiofur equivalents/kg BW administered once daily for five consecutive days in cattle. Scott A. Brown, Joseph F. McAllister, William J. Seaman, Michael J. Prough, and Fabian M. Kausche.

1. Purpose: To describe the injection site morphology at each of the five injection sites (ranging from 10 to 12 hours to 4.5 days after injection) using a slaughter time of 10 to 12 hours after the last of 5 daily subcutaneous injections of ceftiofur sodium at a dose of 2.2 mg ceftiofur equivalents/kg BW administered to cattle.

2. Study Director: Scott A. Brown
   Pharmacia & Upjohn Company
   Animal Health, Drug Metabolism
   7000 Portage Road
   Kalamazoo, MI 49001

3. General Design: This study was conducted in accordance with the GLP regulations and utilized the same animals to establish the injection site and kidney residues.

   a. Test Animals: Bovine/Crossbred beef (6 heifers, 6 steers, plus 1 control heifer).

   b. Dosage Form: Dosage and route of administration: NAXCEL® Sterile Powder (ceftiofur sodium) 2.2 mg/kg (1.0 mg/lb) BW, SC.

   c. Tissues – Injection site.

d. Assay – Visual observation and color photographs of injection sites.

4. Results: The injection of NAXCEL® Sterile Powder at the recommended dose administered SC in the neck of cattle was well tolerated. However, a several square centimeter area of yellow-red discoloration resulting from a single SC injection persisted in many of the cattle beyond 4.5 days post-injection. Also, one of the animals developed an abscess near the injection site.

VI. HUMAN FOOD SAFETY

A. Toxicity and Comparative Metabolism

The toxicity testing of ceftiofur has been summarized in previous FOI Summaries for NAXCEL® (ceftiofur sodium) Sterile Powder (NADA 140-338).

B. Calculation of Safe Concentrations

Derivation of the safe concentrations is in the above-referenced FOI Summaries for NADAs 140-338 and 140-890.

C. Total Residue Depletion and Metabolism Study

The studies conducted to determine total residue depletion and metabolism are summarized in previous FOI Summaries for NAXCEL® (ceftiofur sodium) Sterile Powder (NADA 140-338).

D. Tolerances for Ceftiofur-Derived Residues

Tolerances for ceftiofur derived residues were published in the Federal Register (63 FR 53579, October 6, 1998) and are specified in 21 CFR 556.113. Tolerances for residues of desfuroylceftiofur (marker residue) in edible cattle tissues were established at 8 ppm in kidney (target tissue), 2 ppm in liver, 1 ppm in muscle, and 100 ppb in milk.

E. Residue Depletion and Confirmation of the Tolerance

1. Purpose: An additional study was conducted with NAXCEL® administered SC (SR a0058234) to determine the injection site residues at 10 to 12 hours and at 34 to 36 hours after injection. Kidney residues were also determined at 10 to 12 hours after the last injection, using a slaughter time of 10 to 12 hours after the last of 5 daily injections of ceftiofur sodium administered SC at a dose of 2.2 mg ceftiofur equivalents/kg (1.0 mg/lb) BW to cattle.

2. Study Director: Scott A. Brown
   Pharmacia & Upjohn Company
   Animal Health, Drug Metabolism
   7000 Portage Road
   Kalamazoo, MI

   a. Test Animals: Twelve yearling crossbred beef cattle (6 heifers, 6 steers, and a control heifer).

   b. Dosage Form: NAXCEL® Sterile Powder (ceftiofur sodium) 2.2 mg/kg BW

   c. Route of Administration: Subcutaneous injection

   c. Assay: HPLC - DCA

   d. Tissues: Injection site, kidney

3. Results:

   Table 6.1. Residues (ppm) of ceftiofur in kidney and injection site tissues following subcutaneous administration of ceftiofur sodium, 50 mg ceftiofur equivalents/mL, at a dose of 2.2 mg ceftiofur equivalents/kg body weight for five consecutive days.

Tissue	Ceftiofur concentration (mean ± SD)
Kidney (10 to 12 h post-injection #5)	2.40±0.58
Injection Site #5 (10 to 12 h post-injection)	3.28±3.20
Injection Site #4 (34 to 36 h post-injection)	0.64±0.21

   All residues of ceftiofur and desfuroylceftiofur-related metabolites were less than approximately 10 μg CE/g at the SC injection site 10 to 12 hours after the last of five daily SC doses of ceftiofur sodium of 2.2 mg CE/kg BW. Furthermore, the 99th tolerance limit for kidney residue data from this study (4.56 μg CE/kg) was below the FDA tolerance value for ceftiofur in kidney of 8 μg CE/g. Residues of ceftiofur and desfuroylceftiofur - related metabolites in kidney tissue and at the injection sites 10 to 12 hours after the last of five daily SC doses of ceftiofur sodium at 2.2 mg CE/kg BW are consistent with a zero day withdrawal.

F. Analytical Method for Residues

The residue detection method for the detection of ceftiofur-related residues is based on the cleavage of the disulfide and/or thioester bonds between ceftiofur-related metabolites and their conjugate sulfur-containing moiety using dithioerythritol (DTE) to yield descfuroylceftiofur (DFC). To prevent the formulation of new DCF-conjugates, DFC is treated with iodoacetamide to produce a stable thioacetamide derivative, desfuroylceftiofur acetamide (DCA). DCA is extracted using a C-18 solid-phase extraction (SPE) cartridge and further purified by anion and cation exchange SPE cartridges. DCA is separated using gradient HPLC and detected by UV absorption at 266 nm. DCA concentrations are calculated using the slope and intercept of the calibration line of standards prepared in buffer. Extraction and chromatographic conditions are adapted specifically for each tissue. The following Limits of Detection and Limits of Quantitation are achieved in skeletal muscle (injection site) and kidney as shown in Table 6.2.

Table 6.2. Limits of detection and limits of quantitation for ceftiofur-related residues in kidney and skeletal muscle (injection site)

Tissue	Limit of Detection	Limit of Quantitation
Kidney	0.025 ppm	0.10 ppm
Muscle	0.025 ppm	0.10 ppm

VII. 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 of the implementing regulations. The data demonstrate that NAXCEL® Sterile Powder is safe and effective for the treatment of bovine respiratory disease and foot rot when administered subcutaneously to cattle at a dose of 0.5 to 1.0 mg ceftiofur per kilogram body weight for 3 to 5 days.

According to the Center's supplemental approval policy, 21 CFR 514.106(b)(2)(iv), this is a Category II supplement which required a re-evaluation of the safety and effectiveness data.

Data from a bioequivalence study comparing IM versus SC route of drug administration at a dosage of 1.0 mg ceftiofur/lb body weight was used to support the effectiveness of ceftiofur sodium for the treatment of respiratory disease and foot rot in cattle.

The human food safety data indicates that beef cattle treated with ceftiofur sodium at the highest recommended dose (1.0 mg ceftiofur/lb body weight) by subcutaneous injection will require no withdrawal period for the depletion of ceftiofur from the tissue.

Labeling restricts this drug to use by or on order of a licensed veterinarian. The Center for Veterinary Medicine (CVM) has concluded that this product shall continue to have prescription marketing status.

The agency has determined under 21 CFR 25.33 (a)(1) that this action is of the type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Under Section 512(c)(2)(F)(iii) of the FFDCA, this approval for food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval. The three years of marketing exclusivity applies only to the subcutaneous route of drug administration in cattle provided for in the supplemental application for which this supplement is approved.

NAXCEL® Sterile Powder is under U.S. patent number 4,464,367, which expires August 7, 2001.

VIII. APPROVED PRODUCT LABELING

A copy of the draft facsimile labeling is attached to this document.

A. NAXCEL® Sterile Powder - 1 gram Vial Label

B. NAXCEL® Sterile Powder - 4 gram Vial Label

C. NAXCEL® Sterile Powder - 1 gram Shipper Label

D. NAXCEL® Sterile Powder - 4 gram Shipper Label

E. NAXCEL® Sterile Powder- Package Insert