Approval Date: March 15, 1991

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-338

B. Sponsor

The Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001

C. Proprietary Name

NAXCEL® Sterile Powder

D. Established Name

ceftiofur sodium

E. Dosage Form

NAXCEL Sterile Powder is available in two package sizes: 1 gram and 4 gram vials.

Reconstituted product should be used within 12 hours if stored at controlled room temperature 15° - 30° C (59° - 86° F) or within 7 days if stored in a refrigerator.

1 gram vial
Reconstitute with 20 mL Sterile Water for Injection or with Bacteriostatic Water for Infection. Each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur.

4 gram vial
Reconstitute with 80 mL Sterile Water for Injection or with Bacteriostatic Water for Injection. Each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur.

F. Dosage Regimen

NAXCEL Sterile Solution should be administered by intramuscular injection to cattle at the dosage range of 0.5 to 1.0 mg ceftiofur per pound of body weight (1 to 2 mL reconstituted sterile solution per 100 lb body weight). Treatment should be repeated every 24 hours for a total of three treatments. Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the first three treatments.

G. Indication

NAXCEL Sterile Powder is indicated for treatment of bovine respiratory disease (shipping fever, pneumonia) in beef and dairy cattle. This product may be used in lactating dairy cattle.

H. Effect of Supplement

Provides for the use of ceftiofur sodium (NAXCEL Sterile Powder) in lactating dairy cattle, a new class of animal, for the same indications approved in the parent NADA.

II. EFFECTIVENESS

Effectiveness of NAXCEL Sterile Powder for the treatment of BRD is addressed in the FOI summary dated January 25, 1988, and made available when the NADA was codified on February 24, 1988 (53 FR 5369/70).

III. TARGET ANIMAL SAFETY

Target animal safety is addressed in the FOI summary dated January 25, 1988.

IV. HUMAN FOOD SAFETY

A. Toxicity Tests

Toxicity studies are addressed in the FOI summary dated January 25, 1988. These include mutagenicity, oral feeding and hypersensitivity potential studies. The lowest no-observed-effect-level from the oral feeding studies was 30 mg ceftiofur per kg body weight.

B. Safe Concentrations of Total Residues

Previous determinations have resulted in safe concentrations for total residues of ceftiofur in tissues to be:

- muscle - 3 ppm
- kidney - 9 ppm
- liver - 6 ppm
- fat - 12 ppm

The calculated safe concentration for total residues of ceftiofur in milk is 1 ppm (one third that of muscle).

C. Total Residue and Metabolism Studies

Two 14-C-labeled ceftiofur studies were completed in lactating dairy cattle to 1) determine time to peak concentration of total residues in milk following intramuscular administration of ceftiofur, and 2) determine total residue depletions in milk following last treatment.

In contrast to intramammary treatment, where there is a regular (approximately 12 hour) interval between time of treatment and next milking, intramuscular administration of drug can occur at any time prior to normal milking, therefore, it is relevant to determine time to peak concentration of total residues in milk following IM administration. In the initial study, therefore, one cow (616 kg) in its second lactation received five intramuscular injections of 0.5 mg/lb of 14-C-ceftiofur at 3, 6, 9, or 12 hours prior to the first normal milking. Total residues of ceftiofur were higher (0.045 ppm) at 12 hours after treatment than at any other time interval post treatment. The data from this study provided in tabular form showed that 12 hour intervals post treatment are the critical time periods for the purposes of the residue depletion study.

Table 1. Total Residues (ppm) of Ceftiofur in Milk Following Intramuscular Injection at 0.5 mg (1.1 mg/kg) Ceftiofur Per Pound of Body Weight

Injection Time (hours) Before Normal Milking	Total Residues (ppm) Ceftiofur Equivalents
3	0.0158
6	0.0352
9	0.0393
12	0.0450
15*	0.0350
18*	0.0211
21*	0.0203
24*	0.0189

* includes one milking 12h prior to these milking times

A residue depletion study was then conducted to 1) ascertain total residues of ceftiofur in milk at 12 hour intervals following the last of five daily IM injections and to characterize the residues present in the milk.

Table 2. 14-C Ceftiofur Equivalents (ppm) and Screening Assay Residue Results from Milk of Dairy Cattle Administered Ceftiofur Sodium via Intramuscular Injection Five Consecutive Days at 1.0 mg Ceftiofur per lb (2.2 mg/kg) Body Weight.

Time Post Treatment (Di + h)(1)	14-C Ceftiofur Equivalents (2) (ppm)			Screening Assay Results(3) (Number Animals Positive/ Number Animals Tested)		
	Total	Free	Major Free Metabolite	BSDA	C/P	Delvotest-P®
D1 + 12	0.0825	0.0291	0.0071	0/6	0/6	0/6
D1 + 24	0.0402	--		0/6	0/6	0/6
D2 + 12	.1014	.0367	.0096	0/6	0/6	0/6
D2 + 24	.0466	--		0/6	0/6	0/6
D3 + 12	.1088	.0371	.0096	0/6	0/6	0/6
D3 + 24	.0507			0/6	0/6	0/6
D4 + 12	.1088	.0370	.0091	0/6	0/6	0/6
D4 + 24	.0530			0/6	0/6	0/6
D5 + 12	.1154	. 0383	.0101	0/6	0/6	0/6
D5 + 24	.0598	.0205	.0041	0/6	0/6	0/6
D5 + 36	.0325			0/6	0/6	0/6
D5 + 48	.0201			0/6	0/6	0/6
D5 + 60	.0105			0/6	0/6	0/6
D5 + 72	.0133			0/6	0/6	0/6
D5 + 84	.0110			0/6	0/6	0/6
D5 + 96	.0118			0/6	0/6	0/6
D5 + 108	.0113			0/6	0/6	0/6
D5 + 120	.0095			0/6	0/6	0/6

(1) (Di + h) refers to ith Dose, i = 1 to 5, and h hours after last dose.

(2) 14-C Ceftiofur Equivalents (ppm) refers to 1) total residues of ceftiofur present in milk, 2) free metabolites (non covalently bound to proteins of milk) in milk, and 3) the major free metabolite in milk which is microbiologically active. All tabled values are means from six animals.

(3) -BSDA refers to *Bacillus stearothermophilus* disc assay. -C/P refers to the cylinder/plate assay (*M. luteus*). -Delvotest-P® is a commercial assay.

D. Comparative Metabolism Study Results

In a drug accountability study milk was found to contain less than 0.15 percent of the total dose. Over the same time interval, 120 h, urine and feces accounted for 62.8 and 35.7 percents of the dose, respectively.

Approximately 65 percent of the total residues of milk were bound to macromolecules as a single metabolite (desfuroylceftiofur). This compares with 75 percent of the total residues in kidney which were bound to macromolecules, also as the same metabolite. The free metabolites consisted of polar and non-polar compounds of which one (desfuroylceftiofurcysteine disulfide or DCD) was the single most prevalent metabolite. When total residues were highest in milk (0.115 ppm at 12 h after last daily dosage), the concentration of this metabolite was also at its highest value of 0.01 ppm.

The predominant free metabolite (DCD) in milk has the same HPLC column retention time as a metabolite previously tested in the passive cutaneous anaphylaxis study in guinea pigs to evaluate the hypersensitivity potential of ceftiofur sodium. The concentration of this metabolite in kidney tissue is much higher (~1.3 ppm) than it is in milk (0.01 ppm).

In summary, milk contains no metabolites not heretofore observed in edible tissues of bovine and satisfactorily tested for human safety.

Other comparative metabolism data addressing the IM use of ceftiofur sodium in the bovine are included in the FOI summary dated January 25, 1988.

E. Tolerance for the Market Residue

Total residues at 12 h post last, or any, treatment are substantially lower than the corresponding calculated safe concentration for milk, therefore neither a marker compound nor a tolerance for a marker compound is required.

See FOI summary dated January 25, 1988 for information pertaining to edible tissues other than milk.

F. Study Establishing Withdrawal Period

No milk discard time is required because observed total residues of ceftiofur are well below the calculated safe concentrations at all time intervals post dosing through 120 hours after last treatment.

G. Regulatory Method

A regulatory method is not required.

V. AGENCY CONCLUSIONS

Supplemental Application, Naxcel® sterile powder

The data submitted in support of this supplemental NADA satisfy the requirements of section 512 of the Act and demonstrate that Naxcel is safe and effective when used according to label directions for its proposed use.

This supplemental application provides for the use of ceftiofur sodium (Naxcel® sterile powder) in lactating cattle, a new class of animal in addition to the previously approved use in beef and non-lactating dairy cattle. The firm submitted new residue data for milk in support of this application.

Under the Agency's policy for supplemental approvals, 55 FR 46052, November 1, 1990, this a category II supplement. It required reevaluation of data in the parent application because its approval would increase exposure to residues. The toxicology and metabolism data in the original application meet current standards and additional comparative metabolism work has been done demonstrating that residues in milk have been adequately tested. Because the residues of this product in milk are one tenth of the established safe concentration of 1 ppm at 12 hours post administration, a method to monitor residue levels and a milk withholding time are therefore not required for the safe use of ceftiofur sodium in lactating dairy cattle.

Adequate data pertaining to hypersensitivity issues that are often raised with beta-lactam antibiotics are discussed in the FOI Summary dated January 25, 1988.

This supplemental application does not qualify for a period of exclusivity because investigations supporting approval do not qualify as new clinical or field trials for target animal safety and/or effectiveness.

VI. LABELING

1. Naxcel® package insert
2. Naxcel® 1 gram product label
3. Naxcel® 4 gram product label
4. Naxcel® carton label for 12-1 gram vials
5. Naxcel® carton label for 6-4 gram vials

Copies of these labels may be obtained by writing to the:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.