FREEDOM OF INFORMATION SUMMARY

NAXCEL® Sterile Powder
(ceftiofur sodium)

Supplement to NADA 140-338

"…for the treatment of caprine respiratory disease (goat pneumonia) associated with *Pasteurella haemolytica* and *Pasteurella multocida*."

SUBMITTED BY:

PHARMACIA & UPJOHN

Date of approval - March 7, 2001

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I. GENERAL INFORMATION

NADA Number.	140-338 (Goat)
Sponsor:	Pharmacia & Upjohn 7000 PortageRoad Kalamazoo, Michigan 49001
Generic Name:	Ceftiofur sodium sterile powder
Trade Name:	NAXCEL® Sterile Powder
Marketing Status:	Prescription
Supplemental Effect:	The approval of this supplement will allow for the use of ceftiofur sodium (NAXCEL® Sterile Powder) for the treatment of bacterial pneumonia in goats to be added to the previously approved NAXCEL label.

II. INDICATION FOR USE

NAXCEL® Sterile Powder is indicated for the treatment of caprine respiratory disease (goat pneumonia) associated with *Pasteurella haemolytica* and *Pasteurella multocida*.

III. DOSAGE FORM, ROUTE OF ADMINISTRATION, AND RECOMMENDED DOSAGE

A. Dosage Form: Powder for reconstitution and injection.

B. Route of Administration: Intramuscular injection.

C. Recommended Dosage: 0.5 to 1.0 mg/lb body weight. Treatment should be repeated at 24-hour intervals for 3 consecutive days. Additional treatments may be given on Days 4 and 5 for animals that do not show a satisfactory response after initial 3 treatments.

IV. EFFECTIVENESS

The data for these studies were generated under Public Master File (PMF) 5671, and a notice of availability of this PMF is published in the Federal Register (65 FR 39911, June 28, 2000). The purpose of these studies was to show that the pharmacokinetics of the drug in goats are similar to those in cattle and sheep for whom the drug is already approved. The results of these studies are presented in the following tables.

Table 4.1. Pharmacokinetic values obtained from serum concentrations of ceftiofur and metabolites after intravenous administration of a single dose of ceftiofur sodium at a dose of 1.1 mg ceftiofur free acid equivalents/kg (0.5 mg/lb) in lactating dairy goats.

Parameter	Animal Number							
	1061	**9079**	**9063**	**2032**	**8026**	**9055**	**Mean**	**Std. Dev.**
T½a (min)	26.5	37.1	16.9	36.4	58.0	21.9	28.0	(harmonic)
T½ß (min)	131	166	137	223	389	145	172	(harmonic)
Cp0 (µg/mL)	8.05	6.81	9.79	7.81	8.18	7.06	7.96	1.1
AUC $_{0-\text{>inf}}$ (µg•min/mL)	551	681	762	723	1130	797	774	195
MRT $_{0-\text{>inf}}$ (min)	122	165	160	192	305	182	188	62

Table 4.2. Pharmacokinetic values obtained from serum concentrations of ceftiofur and metabolites after intravenous administration of a single dose of ceftiofur sodium at a dose of 2.2 mg ceftiofur free acid equivalents/kg (1.0 mg/lb) in lactating dairy goats.

Parameter	Animal Number							
	2025	**9047**	**9039**	**9048**	**2058**	**0003**	**Mean**	**Std. Dev.**
T½a (min)	46.0	32.9	54.1	69.4	26.9	45.7	41.6	(harmonic)
T½ß (min)	230	164	305	505	182	221	233	(harmonic)
Cp0 (µg/mL)	13.1	13.8	10.2	13.7	17.4	16.0	14.0	2.5
AUC $_{0-\text{>inf}}$ (µg•min/mL)	1400	1470	1450	2060	1510	1860	1625	270
MRT $_{0-\text{>inf}}$ (min)	192	179	278	345	184	204	230	67

Table 4.3. Pharmacokinetic values obtained from serum concentrations of ceftiofur and metabolites after intravenous administration of a single dose of ceftiofur sodium at a dose of 2.2 mg ceftiofur free acid equivalents/kg (1.0 mg/lb) in non-lactating dairy goats.

Parameter	Animal Number							
	2025	**9047**	**9039**	**9048**	**2058**	**0003**	**Mean**	**Std. Dev.**
T½a (min)	68.9	31.2	46.4	66.6	56.3	41.1	48.0	(harmonic)
T½ß (min)	290	196	227	417	304	200	254	(harmonic)
Cp0 (µg/mL)	14.0	14.5	16.4	16.4	18.2	17.3	16.1	1.6
AUC $_{0-\text{>inf}}$ (µg•min/mL)	1890	1520	2220	2620	2170	1790	2036	383
MRT $_{0-\text{>inf}}$ (min)	209	206	232	336	220	182	231	54

Table 4.4. Pharmacokinetic values obtained from serum concentrations of ceftiofur and metabolites after intramuscular administration of a single dose of ceftiofur sodium at a dose of 1.1 mg ceftiofur free acid equivalents/kg (0.5 mg/lb) in lactating dairy goats.

Parameter	Animal Number							
	1061	**9079**	**9063**	**2032**	**8026**	**9055**	**Mean**	**Std. Dev.**
T½a (min)	20.1	38.7	7.16	42.7	44.0	4.20	12	(harmonic)
T½ß (min)	133	195	124	196	288	133	163	(harmonic)
Cpmax (µg/mL)	1.56	1.74	3.04	4.67	1.66	3.30	2.66	1.24
t_{max} (min)	64.0	127	36.4	28.2	135	29.0	69.9	49.1
AUC $_{0-\text{>inf}}$ (µg•min/mL)	420	730	647	698	966	708	695	175
MRT $_{0-\text{>inf}}$ (min)	220	338	189	197	474	198	269	115
Lag Time (min)		14.2	5.14	5.31		7.44	8.02	4.25

Table 4.5. Pharmacokinetic values obtained from serum concentrations of ceftiofur and metabolites after intramuscular administration of a single dose of ceftiofur sodium at a dose of 2.2 mg ceftiofur free acid equivalents/kg (1.0 mg/lb) in lactating dairy goats.

Parameter	Animal Number							
	2025	**9047**	**9039**	**9048**	**2058**	**0003**	**Mean**	**Std. Dev.**
T½a (min)	14.7	10.5	26.7	23.1	12.9	18.8	16	(harmonic)
T½ß (min)	117	159	2.46	195	91.7	279	156	(harmonic)
Cpmax (µg/mL)	5.15	4.53	3.25	4.85	5.94	3.76	4.57	0.96
t_{max} (min)	56.5	45.9	111	86.9	42.7	78.9	70.4	26.6
AUC $_{0-\text{>inf}}$ (µg•min/mL)	1170	1260	1510	1810	1080	1840	1447	328
MRT $_{0-\text{>inf}}$ (min)	190	2.45	394	314	151	430	287	112
Lag Time (min)	6.09	1.71	15.1	6.35	0.31	0.39	5.0	5.7

Summary of Pharmacokinetic Results:

A. Despite the dose-related difference in half life values, the dose proportionality was observed in AUC and CMAX values following both IM and IV drug administration. Accordingly, users may be advised that a doubling of the dose will result in a doubling of the systemic ceftiofur concentrations.

B. Single dose pharmacokinetic estimates can be used to predict the serum total ceftiofur concentrations obtained upon multiple IM administrations of ceftiofur sodium in goats.

C. Ceftiofur kinetics are significantly affected by lactation. Drug exposure appears to be significantly less in lactating as compared to dry goats. This difference in exposure appears to be attributable to a faster elimination rate in lactating animals. It is not clear whether this faster elimination is associated with loss in milk versus some other mechanism since less than 1% of the total ceftiofur dose was eliminated in goat milk.

V. ANIMAL SAFETY

A safety/toxicity study conducted in healthy goats with ceftiofur sodium under PMF 5671 demonstrated no drug related adverse effects even when administered IM at up to 5 times the label dose for three times the indicated treatment period. There were no signs of local irritation or systemic toxicity seen in any of the animals. This is consistent with other studies conducted in sheep. Those studies included animal necropsy and injection site examination, which were not necessary in this study since no adverse signs were observed. A notice of availability of this data in PMF 5671 is published in the FEDERAL REGISTER (65 FR 39911, June 28, 2000).

VI. HUMAN FOOD SAFETY

The human food safety data was generated under National Research Support Project 7 (NRSP-7) and the results are addressed in the FOI Summary for PMF 5671 which is published in the Federal Register (65 FR 39911, June 28, 2000)

A. Total Residue Depletion: The human food safety data indicated that goats (non-lactating and lactating) treated with ceftiofur sodium at the highest recommended dose will require no withdrawal period for the depletion of ceftiofur sodium residue from edible tissue. Therefore, the tissue residue data support a zero withdrawal for the use of ceftiofur at doses up to 2.2 mg/kg for five days in goats.

B. Milk Residue Depletion: The human food safety data indicated that lactating goats treated with ceftiofur sodium at the highest recommended dose will require no withdrawal period for the depletion of ceftiofur sodium residue from milk. Therefore, the milk residue data support a zero milk discard for the use of ceftiofur at doses up to 2.2 mg/kg for five days in lactating dairy goats.

C. Regulatory Method: The official regulatory analytical method for residues of desfuroylceftiofur in tissues is the HPLC-DCA-BF method. The official analytical method for residues of desfuroylceftiofur in milk is the HPLC-DCA-RE assay.

VII. AGENCY CONCLUSIONS

The data submitted in support of this supplemental NADA comply with the requirements of Section 512 of the Food, Drug, and Cosmetic Act and 21 CFR 514.1 of the implementing regulations. The data demonstrate that NAXCEL® Sterile Powder (ceftiofur sodium), when used under labeled conditions of use is safe and effective for the treatment of goat respiratory disease (pneumonia) associated with *Pasteurella haemolytica* and *Pasteurella multocida*.

In accordance with 21 CFR 514.106(b)(2)(vii), this is a Category II change. This supplement provides for the use of ceftiofur sodium in goat, a new animal species. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

Data from pharmacokinetic studies in goats, as well as data from studies in cattle (major species) and sheep (minor species) were utilized to support the effectiveness of ceftiofur sodium at the dosage range of 0.5 to 1.0 mg ceftiofur/lb body weight administered intramuscularly once every 24 hours for 3 to 5 days for the treatment of goat respiratory disease. The recommended dosage range (0.5 to 1.0 mg/lb) gives the practitioner greater flexibility of using the drug based on his/her clinical judgment.

The human food safety data demonstrate that when ceftiofur sodium is administered to goats at doses up to 2.2 mg ceftiofur free acid equivalents/kg body weight, neither a milk discard period nor a pre-slaughter withdrawal period is required.

The product remains a prescription drug for safe and effective use by a veterinarian for the treatment of properly diagnosed pneumonia in goats.

The agency has carefully considered the potential environmental effects of this action and has concluded that the action qualifies for a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.33(d)(4). Therefore, neither an environmental assessment nor an environmental impact statement is required

Under Section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval does not qualify for marketing exclusivity because it does not contain reports of new clinical or field investigations (other than bioequivalence or residue studies) or human food safety studies (other than bioequivalence or residue studies) essential to the approval and conducted or sponsored by the applicant.

Ceftiofur is under U.S. patent number 4,464,367 expiring August 7, 2001.

VIII. APPROVED PRODUCT LABELING

A. Proposed R_x labeling for 1- and 4-gram vials.

B. Package insert