Approval Date: October 25, 1996

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-338

B. Sponsor

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, Michigan 49001

C. Proprietary Name

Naxcel® Sterile Powder

D. Established Name

ceftiofur sodium

E. Dosage Form

NAXCEL Sterile Powder is available in 1- and 4-gram vials. When reconstituted according to label instructions, each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur.

F. Dosage Regimen

Administer NAXCEL Sterile Powder to sheep at the dosage of 0.5 to 1.0 mg/lb body weight (1 to 2 mL reconstituted sterile solution per 100 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 which do not show a satisfactory response after initial 3 treatments.

G. Route of Administration

intramuscular (I.M.) injection

H. Indication

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

I. Effect of Supplement

The approval of this supplement will allow for the use of ceftiofur sodium (NAXCEL Sterile Powder) for the treatment of bacterial pneumonia in sheep.

II. EFFECTIVENESS

Section 514.1(d) of Title 21 of the Code of Federal Regulations (CFR) permits extrapolation of data from a major species to a minor species to satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act with respect to the effectiveness of a new animal drug. A combination of data from sheep (a minor species) and a closely-related approved major species (cattle) were used to support the determination of effectiveness, consistent with the Guidelines for the Preparation of Data to Satisfy the Requirements of Section 512 of the Act Regarding Minor Use of Animal Drugs (FDA/CVM April 1986). The efficacy of NAXCEL Sterile Powder for the treatment of bovine respiratory disease associated with *Pasteurella haemolytica*, *Pasteurella multocida*, and *Haemophilus somnus* is documented in the FOI Summary for the January 25, 1988, original approval of NADA 140-338.

Section II.B. of the 1986 minor species guideline, Drugs for Systemic Disease in Minor Domestic Ruminant Species (Sheep and Goats), Part 1. EFFECTIVENESS, offers a case-by-case consideration of bioequivalence when the label claims (indications) are identical (including genus and species of bacteria). For the purposes of this supplement for use in sheep, a determination of medical equivalence was based on: 1) a literature discussion of the similarity of bacterial respiratory disease in sheep and cattle; 2) a pharmacokinetic comparison demonstrating that plasma concentrations of ceftiofur sodium and its metabolites are similar and that therapeutic levels are achieved in both species; and 3) a microbiological survey demonstrating the similarity of susceptibility to ceftiofur in bacteria isolated from clinical cases of respiratory disease in both species.

A. Bacterial respiratory disease in sheep and cattle (bacterial pneumonia):

The rationale for utilizing cattle data to support efficacy in sheep is based, in part, upon the clinical similarities of bacterial pneumonia in these two ruminant species, e.g., identical pathogens, similar disease pathogenesis, and common clinical signs. The pathogenesis of pneumonic pasteurellosis (bacterial pneumonia) in sheep is similar to pneumonic pasteurellosis of cattle.(1,2) An acute fibrinous bronchopneumonia is accompanied by pleurisy. Infection may be caused by *Pasteurella multocida* and/or *P. haemolytica* along with parainfluenza-3 (PI3) virus which may affect the clearance mechanism in the lungs allowing pneumonia to develop.(1,3)

1. Veterinary Medicine, Blood and Radostits, Bailliere Tindall, Phila. (1989), pp 659 and 673
2. Current Veterinary Therapy: Food Animal Practice, J.L. Howard (ed.), W.B. Saunders, Phila. (1981), pp 179 and 184
3. Newsom's Sheep Diseases, H. Marsh, Williams & Wilkins, Baltimore (1965), pp 324-326

The disease is manifested most often in sheep and cattle when animals are subjected to stressful situations such as weaning, housing in drafty or poorly ventilated buildings, exposure to severe weather conditions, transport to feed lots, and malnutrition.(1) Pneumonic pasteurellosis (bacterial pneumonia) is characterized in sheep and cattle by elevated temperature, ocular and nasal discharge, depression, cough, respiratory distress, anorexia , reluctance to move and ultimately mortality in 1 to 5% of affected animals unless medical intervention occurs.(1)

B. Bioavailability of ceftiofur sodium in sheep and cattle:

The bioavailability of ceftiofur sodium and metabolites in sheep was established in a pharmacokinetic study that compared plasma concentrations of ceftiofur and desfuroylceftiofur metabolites after intravenous or intramuscular administration of 0.5 or 1.0 mg ceftiofur free acid equivalents/lb of body weight (TR #815-7926-94-007). Data from this pharmacokinetic study were compared to similar data generated in cattle (TR #788-9760-88-018). Plasma concentrations of ceftiofur and desfuroylceftiofur metabolites in sheep and cattle were comparable at 24 hours (the dosing interval approved for ceftiofur sodium in cattle and the dosing interval proposed for the drug in sheep). Due to an increased total body clearance in sheep as compared to cattle, the maximum serum concentrations in sheep was less than maximum serum concentrations in cattle. However, plasma concentrations at 24 hours were several fold above the MIC90 for the target pathogens (<0.06 g/mL) in both sheep and cattle. The dosage regimen of 0.5 to 1.0 mg/lb of body weight in sheep provides therapeutic plasma concentrations for the target pathogens for the dosing interval (24 hr).

The data for this pharmacokinetic study in sheep was generated under Public Master File (PMF) 5544 and a notice of availability of this PMF is published in the FEDERAL REGISTER (61 FR 49327, Sept. 19, 1996). The pharmacokinetic data from sheep were compared to historical cattle pharmacokinetic data and the results are presented in Table 4.1 and Table 4.2.

Table 4.1. Comparison of two pharmacokinetic studies of ceftiofur sodium, one in sheep (TR #815-7926-94-007) and one in cattle (TR #788-9760-88-018)

Parameters	**Sheep**	**Cattle**
Location	California	France
Dates of Conduct	1992	1988
Time of Last Blood Sample	24 hr	120 hr
Dose (mg/lb)	0.5 and 1.0	0.45
Method of analysis	HPLC-DCA	HPLC-DCA
Trapezoidal AUC calculated to the point listed...	24 hr	Limit of quantitation of the assay
tmax reporting	range	mean SD

Table 4.2. Comparison of pharmacokinetic values after intramuscular administration of ceftiofur sodium in sheep (TR #815-7926-94-007) and in cattle (TR #788-9760-88-018)

Pharmacokinetic Value	**Sheep**	**Cattle**
Dose (mg/lb)	0.5 mg/lb once	0.45 mg/lb once
Cmax (µg/mL)	4.33 ± 1.21	4.12 ± 0.84
C(24) (µg/mL)	0.18 ± 0.06	0.29 ± 0.08
AUC(0-24) (µg °h/mL)	20.2 ± 3.58	29.4 ± 5.56
tmax (h, range)	0.167 - 1.0	0.5 - 1.0

Summary of pharmacokinetic results: Plasma concentrations at 24 hr (the dosing interval approved for ceftiofur sodium in cattle and the dosing interval proposed for the drug in sheep) were several times greater than the MIC for the targeted pathogens (<0.06 µg/mL) in both cattle and sheep. It can be concluded that the dosage regimen of 0.5 to 1.0 mg/lb in sheep provides therapeutic concentrations

(i.e., concentrations above the MIC) for the targeted pathogens for the entire dosing interval. It should also be noted that due to an increased total body clearance in sheep as compared to cattle, the maximum serum concentrations in sheep will be less than maximum serum concentrations in cattle. A lower serum concentration in sheep would not impact on efficacy because the plasma concentrations of ceftiofur at 24 hours should correlate with the reported MIC90 values for the targeted pathogens. Therefore, the dose of ceftiofur sodium in sheep is 0.5 to 1.0 mg/lb (1.1 to 2.2 mg/kg) body weight administered intramuscularly once daily for 3 to 5 days.

C. In vitro susceptibility of bacterial pathogens to ceftiofur sodium:

In vitro susceptibility of sheep respiratory disease pathogens to ceftiofur was established and expressed as Minimum Inhibitory Concentrations for 90% of the isolates (MIC90). Test pathogens were isolated from the lungs and from tracheal washes from sheep in a two-country five-location clinical study (TR #815-9690-93-001). The MIC90 of ceftiofur against P. multocida isolates (n = 23) was 0.031 µg/mL and against *P. haemolytica* isolates (n = 39) was 0.125 µg/mL. These data provide evidence of the susceptibility of sheep respiratory disease pathogens to ceftiofur.

MIC90 values for ceftiofur against *P. multocida* and *P. haemolytica* from a four-year survey of antimicrobial susceptibility trends for isolates from bovine respiratory diseases in North America shows no changes in the susceptibility of these pathogens to ceftiofur. Over the four years of this survey, the MIC90 for these pathogens continues to be 0.06 µg/mL. This study included 318 isolates of *P. multocida* and 461 isolates of *P. haemolytica* that had been recovered from the lungs of cattle that had expired from acute BRD (TR #705-7923-93-005).

D. Conclusions:

The sheep indication, "...for the treatment of sheep respiratory disease (sheep pneumonia) associated with *Pasteurella haemolytica* and *Pasteurella multocida*," is considered identical to the approved bovine indication under current guidelines. The clinical diseases in the two species are similar. Pharmacokinetic data adequately demonstrated the comparable bioavailability of ceftiofur sodium in sheep and cattle after I.M. administration of 0.5 and 1.0 mg/kg dosages. Plasma concentrations of ceftiofur at 24 hours were above the reported MIC90 values for the targeted pathogens. In vitro susceptibility of *P. haemolytica* and *P. multocida* from sheep to ceftiofur are in the same MIC90 range of the same pathogens of bovine origin. Accordingly, NAXCEL Sterile Powder (ceftiofur sodium) is considered effective for the treatment of sheep respiratory disease (sheep pneumonia) associated with *Pasteurella haemolytica* and *Pasteurella multocida*, when used according to label instructions.

III. TARGET ANIMAL SAFETY

A safety/toxicity study conducted in sheep with ceftiofur sodium under PMF 5544 demonstrated wide margin of safety when administered IM to sheep at doses up to 5x the maximum recommended dose of 1.0 mg/lb of body weight and for 3x the recommended duration of treatment. A notice of availability of this data in PMF 5544 is published in the FEDERAL REGISTER (61 FR 49327, September 19, 1996).

IV. HUMAN FOOD SAFETY

A. Toxicity Tests:

All issues concerning toxicity testing of ceftiofur are addressed in the previous Freedom of Information (FOI) Summary for NADA 140-338 for bovine respiratory disease, the approval notice of which appeared in the FEDERAL REGISTER. This summary was updated in August 1993.

B. Safe Concentration of Total Residues:

1. No Observed Effect Level (NOEL): As referenced in the above-mentioned FOI Summary for NADA 140-338, the lowest NOEL from the 90-day oral feeding studies in both dogs and rats is 30 mg ceftiofur equivalents/kg of body weight.
2. Safe Concentration (SC) Calculations: As referenced in the above-mentioned FOI Summary for NADA 140-338, the Acceptable Daily Intake (ADI) of total residues has been established at 1.8 mg/adult/day.

   The revised General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals (FDA-CVM; July 1994) provides for the reservation of a portion of the ADI for milk. Since ceftiofur sodium is approved for parenteral use in lactating dairy cattle, a portion of the ADI must be allotted for ceftiofur residues in milk with the remainder for tissue residues. Thus, 28% of the total ADI (1.8 mg/60 kg adult/day) is reserved for milk and the remainder (73%) for tissue. This results in the following milk and tissue ADI values.

   ADI (milk)
   = 28% x total ADI
   = 27% x 1.8 mg/adult/day
   = 0.5 mg/adult/day

   ADI (tissue)
   = 73% x total ADI
   = 73% x 1.8 mg/adult/day
   = 1.3 mg/adult/day

   Using the revised food consumption factors, the permitted safe concentrations for total residues in edible tissues from sheep are as follows in Table 6.1.

   Table 6.1. Safe Concentrations (SC) for total residues of ceftiofur in edible tissues of sheep using the revised food consumption factors

Tissue	**Daily consumption (g)**	**Safe Concentration (ppm)**
Muscle (non-injection)	300	4.33
Liver	100	13.0
Kidney	50	26.0
Fat	50	26.0

3. Threshold Assessment: See FOI Summary for NADA 140-338 for bovine respiratory disease, as updated August 1993.

C. Total Residue Depletion and Metabolism Study:

This study was completed under the National Research Support Project 7 (NRSP-7). Results are addressed in the FOI Summary for PMF 5544, the availability of which was published in the FEDERAL REGISTER (61 FR 49327, Sept. 19, 1996).

D. Withdrawal Time:

The total residue data demonstrated that the mean concentrations of total ceftiofur residues at 12 hour after the last injection ("zero-day withdrawal") were below the permitted safe concentration in the edible tissues of sheep treated intramuscularly with the maximum dose of 2.2 mg ceftiofur free acid equivalents/kg body weight for 5 days. Therefore, a withdrawal period is not required and a target tissue, marker residue and tolerance have not been designated.

E. Regulatory Method:

Because the total residue data supported a zero-day withdrawal, a regulatory analytical method is not required for the use of ceftiofur sodium in sheep.

V. 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 sheep respiratory disease (pneumonia) associated with *Pasteurella haemolytica* and *Pasteurella multocida*.

According to the Center's supplemental approval policy, 21 CFR 514.1(b)(2)(vii), this is a Category II change. This supplement provides for the use of ceftiofur sodium in sheep, 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.

The human food safety data indicate that sheep treated with ceftiofur sodium at the highest recommended dose will require no withdrawal period for the depletion of ceftiofur residue from the tissue.

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

The agency has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact (FONSI) and the evidence supporting that finding contained in an environmental assessment may be seen in the Dockets Management Branch (HFA-305), Park Building (Room 1-23), 12420 Parklawn Drive, Rockville, Maryland 20855.

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 substantial evidence of the effectiveness of the drug involved, any studies of animal

safety or human food safety (other than bioequivalence or residue studies) required for the approval and conducted or sponsored by the applicant.

The patent number for this drug is 4,464,367 expiring August 7, 2007.

VI. APPROVED PRODUCT LABELING

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

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

Attachments:

1) FOI Summary for PMF 5544
2) FONSI and Environmental Assessment

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.