Date of Approval: December 31, 2003

FREEDOM OF INFORMATION SUMMARY

Supplement to NADA 140-338

NAXCEL Sterile Powder
(ceftiofur sodium)

"For updating the package insert by providing additional clinical microbiology data"

SPONSORED BY:

PHARMACIA & UPJOHN

Table of Contents

1. GENERAL INFORMATION:

a. File Number: NADA 140-338

b. Sponsor: Pharmacia & Upjohn Co.
7000 Portage Rd.
Kalamazoo, MI 49001-0199
Drug Labeler Code: 000009

c. Established Name: ceftiofur sodium

d. Proprietary Name: NAXCEL Sterile Powder

e. Dosage Form: Sterile powder for reconstitution

f. How Supplied: 1 gram and 4 gram vials

g. How Dispensed: R_x

h. Amount of Active Ingredient: Each mL of the reconstituted solution contains ceftiofur sodium equivalent to 50 mg ceftiofur.

i. Route of Administration: intramuscular (IM) and subcutaneous (SC) injections

j. Species/class: cattle, swine, sheep, goats, dogs, horses, day-old chickens, and day-old turkey poults

k. Recommended Dosage:

Cattle: 0.5 to 1.0 mg ceftiofur/lb body weight IM or SC.

Swine: 1.36 to 2.27 mg ceftiofur/lb body weight IM only.

Sheep: 0.5 to 1.0 mg ceftiofur/lb body weight IM only.

Goat: 0.5 to 1.0 mg ceftiofur/lb body weight IM only.

Horse: 1 to 2 mg ceftiofur/lb body weight IM only.

Dog: 1 mg/lb body weight SC only.

Day-old chick: 0.08 to 0.20 mg ceftiofur/chick once in the neck SC only.

Day-old turkey poult: 0.17 to 0.5 mg ceftiofur/poult once in the neck SC only.

l. Pharmacological Category: antimicrobial

m. Indications:

Cattle:	NAXCEL Sterile Powder is indicated for the treatment of bovine respiratory disease (shipping fever, pneumonia) associated with *Mannheimia haemolytica, Pasteurella multocida* and *Haemophilus somnus*. NAXCEL Sterile Powder is also indicated for treatment of acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.
Swine:	NAXCEL Sterile Powder is indicated for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus (Haemophilus) pleuropneumoniae, Pasteurella multocida, Salmonella choleraesuis* and *Streptococcus suis* type 2.
Sheep:	NAXCEL Sterile Powder is indicated for treatment of sheep respiratory disease (sheep pneumonia) associated with *Mannheimia haemolytica* and *Pasteurella multocida.*
Goat:	NAXCEL Sterile Powder is indicated for treatment of caprine respiratory disease (goat pneumonia) associated with *Mannheimia haemolytica* and *Pasteurella multocida.*
Horse:	NAXCEL Sterile Powder is indicated for the treatment of respiratory infections in horses associated with *Streptococcus zooepidemicus.*
Dog:	NAXCEL Sterile Powder is indicated for the treatment of canine urinary tract infections associated with *Escherichia coli* and *Proteus mirabilis.*
Day-old Chicken:	NAXCEL Sterile Powder is indicated for the control of early mortality, associated with *Escherichia coli* organisms susceptible to ceftiofur, in day-old chicks.

Day-old Turkey Poult: NAXCEL Sterile Powder is indicated for the control of early mortality, associated with *Escherichia coli* organisms susceptible to ceftiofur, in day-old turkey poults.

n. Effect of this Supplement: This supplement provides four specific changes to the product insert, 1) revision of the "clinical microbiology" section to update the MIC table using the new MIC data for ceftiofur, 2) the addition of a table listing acceptable quality control ranges for ceftiofur, 3) the addition of the latest National Committee for Clinical Laboratory Standards (NCCLS) reference at the end of the insert, and 4) clarification of the statement under "Storage Conditions" dealing with the storage of reconstituted Naxcel via freezing.

2. EFFECTIVENESS:

Updated *in vitro* minimum inhibitory concentration (MIC) data for cattle, swine, sheep, chicken, and turkey pathogens are presented in tabular format in the labeling for NAXCEL Sterile Powder.

In the revised package insert, MIC data for bacterial isolates collected during clinical field studies have been placed in Table 1. Bacterial isolates collected over time, including those collected from diagnostic laboratories in the US and Canada as part of a surveillance program, are in Table 2. MICs were determined using a commercially available broth microdilution system that conforms to the guidelines for the National Committee for Clinical Laboratory Standards (NCCLS) broth microdilution method. Data from the QA organisms tested with each run are included in each study report.

In the clinical field studies isolate table (Table 1), data previously included on the EXCENEL RTU (NADA 140-890) package insert is now included in the NAXCEL package insert. Table 1 is the updated table with data for all bacterial isolates collected during clinical field studies.

Table 1. Ceftiofur MIC values of bacterial isolates from clinical field studies in the USA

Animal	Organism	Number Tested	Date Tested	MIC_{90}* (μg/mL)	MIC Range (μg/mL)
Bovine	*Mannheimia haemolytica*	461	1988-1992	0.06	≤ 0.03-0.13
	Mannheimia haemolytica	42	1993	0.015	≤ 0.003-0.03
	Pasteurella multocida	318	1988-1992	0.06	≤ 0.03-0.25
	Pasteurella multocida	48	1993	≤ 0.003	≤ 0.003-0.015
	Haemophilus somnus	109	1988-1992	0.06	≤ 0.03-0.13
	Haemophilus somnus	59	1993	≤ 0.0019	no range
	Fusobacterium necrophorum	17	1994	≤ 0.06	no range
Swine	*Actinobacillus pleuropneumoniae*	83	1993	≤ 0.03	≤ 0.03-0.06
	Pasteurella multocida	74	1993	≤ 0.03	≤ 0.03-0.06
	Streptococcus suis	94	1993	0.25	≤ 0.03-1.0
	Salmonella choleraesuis	50	1993	1.0	1.0-2.0
	Beta hemolytic streptococcus spp.	24	1993	≤ 0.03	≤ 0.03-0.06
	Actinobacillus suis	77	1998	0.0078	0.0019-0.0078
	Haemophilus parasuis	76	1998	0.06	0.0039-0.25
Sheep	*Mannheimia haemolytica*	39	1992	0.13	≤ 0.03-0.13
	Pasteurella multocida	23	1992	≤ 0.03	no range
Canine	*Escherichia coli*	44	1992	4.0	0.06-64.0
	Escherichia coli	18	1990	0.25	0.13-0.5
	Proteus mirabilis	17	1990	≤ 0.06	≤ 0.06-0.5
	Proteus mirabilis	23	1992	1.0	≤ 0.06-4.0
Turkey	*Escherichia coli*	1204	1995	1.0	0.13->32.0

*Minimum inhibitory concentration (MIC) for 90% of the isolates.

The diagnostic lab isolate table (Table 2) contains some MIC data that were previously included on the NAXCEL package insert. The remaining data are from study reports from the last four years of a surveillance program and other MIC surveys.

Table 2. Ceftiofur MIC values of bacterial isolates from diagnostic laboratories* in the USA and Canada

Animal	Organism	Number Tested	Date Tested	MIC_{90}** (µg/mL)	MIC Range (µg/mL)
Bovine	*Mannheimia haemolytica*	110	1997-1998	0.06	≤ 0.03-0.25
	Mannheimia haemolytica	139	1998-1999	≤ 0.03	≤ 0.03-0.5
	Mannheimia haemolytica	209	1999-2000	≤ 0.03	≤ 0.03-0.12
	Mannheimia haemolytica	189	2000-2001	≤ 0.03	≤ 0.03-0.12
	Pasteurella multocida	107	1997-1998	≤ 0.03	≤ 0.03-0.25
	Pasteurella multocida	181	1998-1999	≤ 0.03	≤ 0.03-0.5
	Pasteurella multocida	208	1999-2000	≤ 0.03	≤ 0.03-0.12
	Pasteurella multocida	259	2000-2001	≤ 0.03	≤ 0.03-0.12
	Haemophilus somnus	48	1997-1998	≤ 0.03	≤ 0.03-0.25
	Haemophilus somnus	87	1998-1999	≤ 0.03	≤ 0.03-0.125
	Haemophilus somnus	77	1999-2000	≤ 0.03	≤ 0.03-0.06
	Haemophilus somnus	129	2000-2001	≤ 0.03	≤ 0.03-0.12
	Bacteroides fragilis group	29	1994	16.0	≤ 0.06->16.0
	Bacteroides spp., non-fragilis group	12	1994	16.0	0.13->16.0
	Peptostreptococcus anaerobius	12	1994	2.0	0.13-2.0
Swine	*Actinobacillus pleuropneumoniae*	97	1997-1998	≤ 0.03	no range
	Actinobacillus pleuropneumoniae	111	1998-1999	≤ 0.03	≤ 0.03-0.25
	Actinobacillus pleuropneumoniae	126	1999-2000	≤ 0.03	≤ 0.03-0.06
	Actinobacillus pleuropneumoniae	89	2000-2001	≤ 0.03	≤ 0.03-0.06
	Pasteurella multocida	114	1997-1998	≤ 0.03	≤ 0.03-1.0
	Pasteurella multocida	147	1998-1999	≤ 0.03	≤ 0.03-0.5
	Pasteurella multocida	173	1999-2000	≤ 0.03	≤ 0.03-0.06
	Pasteurella multocida	186	2000-2001	≤ 0.03	≤ 0.03-0.12
	Streptococcus suis	106	1997-1998	0.5	≤ 0.03-4.0
	Streptococcus suis	142	1998-1999	0.25	≤ 0.03-1.0
	Streptococcus suis	146	1999-2000	0.06	≤ 0.03-4.0
	Streptococcus suis	167	2000-2001	0.06	≤ 0.03-4.0
	Salmonella choleraesuis	96	1999-2000	1.0	0.03->4.0
	Salmonella choleraesuis	101	2000-2001	1.0	0.5-2.0
	Erysipelothrix rhusiopathiae	44	2002	≤ 0.03	≤ 0.03-0.06
Equine	*Streptococcus equi* subsp. *equi*	12	1994	≤ 0.0019	no range
	Streptococcus zooepidemicus	48	1994	≤ 0.0019	no range
	Rhodococcus equi	66	1998	4.0	≤ 0.03-16.0
	Bacteroides fragilis group	32	1995	> 16.0	0.13->16.0

Table 2 (cont'd). Ceftiofur MIC values of bacterial isolates from diagnostic laboratories* in the USA and Canada

Animal	Organism	Number tested	Date tested	MIC_{90}** (µg/mL)	MIC range (µg/mL)
Equine	*Bacteroides* spp., non-fragilis group	12	1995	4.0	0.25-4.0
	Fusobacterium necrophorum	16	1995	≤ 0.06	no range
Canine	*Escherichia coli*	26	2000	32	0.25->32
	Proteus mirabilis	14	2000	0.25	0.06-0.25
Turkey	*Escherichia coli*	17	1998-1999	1.0	0.25-1.0
	Escherichia coli	25	1999-2000	0.50	0.12-0.50
	Escherichia coli	20	2000-2001	2.0	0.12-16
	Citrobacter spp.	37	1995	32.0	0.5->32.0
	Enterobacter spp.	51	1995	> 32.0	0.13->32.0
	Klebsiella spp.	100	1995	1.0	0.13-2.0
	Proteus spp.	19	1995	1.0	0.06-32.0
	Pseudomonas spp.***	31	1995	>32.0	0.06->32.0
	Salmonella spp.	24	1995	1.0	0.5-1.0
	Staphylococcus spp. (coagulase-positive)	17	1995	2.0	1.0-2.0
	Staphylococcus spp. (coagulase-negative)	26	1995	8.0	0.13->32.0
Chicken	*Escherichia coli*	62	1997-1998	0.50	0.25-2.0
	Escherichia coli	53	1998-1999	4.0	0.25->4
	Escherichia coli	67	1999-2000	0.50	0.12-16
	Escherichia coli	90	2000-2001	1.0	≤ 0.03-8

*The following *in vitro* data are available but their clinical significance is unknown.
**Minimum inhibitory concentration (MIC) for 90% of the isolates.
***MIC_{50} is 32 µg/mL

Based on the pharmacokinetic studies of ceftiofur in swine and cattle after a single intramuscular injection of 1.36 to 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) body weight (swine) or 0.5 to 1.0 mg ceftiofur equivalents/lb (1.1 to 2.2 mg/kg) BW (cattle) and the MIC and disk (30 µg) diffusion data, the following breakpoints are recommended by NCCLS.

Zone diameter (mm)	MIC (µg/mL)	Interpretation
≥ 21	≤ 2	(S) Susceptible
18-20	4.0	(I) Intermediate
≤ 17	≥ 8.0	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate" is a technical buffer zone and isolates falling into this category should be retested. Alternatively the organism may be successfully treated if infection is in a body site where the drug is physiologically concentrated. A report of "Resistant" indicates that the achievable drug concentrations are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures recommended by NCCLS require the use of laboratory control organisms for both diffusion techniques and dilution techniques. The 30 µg ceftiofur sodium disk should give the following zone diameters and the ceftiofur sodium standard reference powder (or disk) should provide the following MIC values for the reference strains (Table 3). Ceftiofur sodium disk or powder reference standard is appropriate for both ceftiofur salts.

Table 3. Acceptable quality control ranges for ceftiofur against National Committee for Clinical Laboratory Standards recommended American Type Culture Collection (ATCC) reference strains

Organism Name (ATCC Number)	Zone Diameter * (mm)	MIC Range (µg/ml)
Escherichia coli (25922)	26-31	0.25-1.0
Staphylococcus aureus (29213)	--	0.25-1.0
Staphylococcus aureus (25923)	27-31	--
Pseudomonas aeruginosa (27853)	14-18	16.0-64.0
Actinobacillus pleuropneumoniae (27090)	34-42**	0.004-0.015***
Haemophilus somnus (700025)	36-46**	0.0005-0.004***

*All testing performed using a 30 µg disk.

** Quality control ranges are applicable only to tests performed by disk diffusion test using a chocolate Mueller-Hinton agar, incubated in 5-7% CO_2 for 20-24 hours.

***MIC quality control ranges are applicable only to tests performed by broth microdilution procedures using veterinary fastidious medium (VFM).

The references supporting the data provided in the revised clinical microbiology tables are listed below.

a. Portis, E.S., S.A. Salmon, C.A. Case, J.L. Watts. Results of 1997-1998 resistance monitoring program for premafloxacin with veterinary pathogens. Pharmacia & Upjohn Study Report a0032820, 9 February 1999.

b. Portis, E.S., S.A. Salmon, C.A. Case, J.L. Watts. Results of 1998-1999 susceptible monitoring program for premafloxacin with veterinary pathogens. Pharmacia & Upjohn Study Report a0086065, 19 September 2000.

c. Portis, E.S., S.A. Salmon, C.A. Case. Results of 2000 susceptibility monitoring program for ceftiofur with veterinary pathogens. Pharmacia Animal Health Study Report a0097495, 27 June 2001.

d. Portis, E.S., S.A. Salmon, C. Lindeman, C.A. Case. Results of 2001 susceptibility monitoring program for ceftiofur with veterinary pathogens. Pharmacia Animal Health Study Report SR-0829-7922-2002-006, 20 August 2002.

e. Lindeman, C., S.A. Salmon, E.S. Portis, C.A. Case. Minimum inhibitory concentration determinations for ceftiofur and comparators against *Erysipelothrix rhusiopathiae* isolated from pigs in Iowa. Pharmacia Animal Health Study Report SR-0788-7922-2002-001, 1 July 2002.

f. Portis, E.S., S.A. Salmon. Minimum inhibitory concentration determinations for ceftiofur, desfuroylceftiofur, and cefpodoxime against bacterial pathogens of canines. Pharmacia Animal Health Study Report SR-0850-7922-2002-001, 24 June 2002.

g. Salmon, S.A., J.L. Watts. Minimum inhibitory concentration determinations for various antimicrobials agents against 1570 bacterial isolates from turkey poults. 2000. *Avian Diseases*. **44**:85-98.

CONCLUSIONS:

The updated clinical microbiology tables provide the following:

a. Updated clinical microbiology data and interpretive criteria for cattle and swine.
b. An insert format that is user friendly by having all of the important information for a particular animal species in one section of the table, with isolates supported by clinical data in a separate table from isolates collected from diagnostic laboratories.
c. The practicing veterinarian will have more information that can be readily located on the insert to assist in making sound recommendations for the use of NAXCEL Sterile Powder.

3. TARGET ANIMAL SAFETY:

This supplement to NADA 140-338 does not change the target animal safety data for this product.

4. HUMAN FOOD SAFETY:

This supplement to NADA 140-338 does not change the human food safety data for this product.

5. AGENCY CONCLUSIONS:

The data submitted in support of this supplemental NADA satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514.1 of the implementing regulations. The updated clinical microbiology data presented in the product insert is user friendly by having all the important use information for a particular animal species in one section of the insert. As a result, the practicing veterinarian will have more information that can be readily located on the insert to assist in making sound therapy recommendations for the use of NAXCEL Sterile Powder.

The product remains a prescription drug for safe and effective use by a veterinarian in the treatment of diseases in cattle, swine, sheep, goats, dogs, horses, day-old chicks and day-old turkey poults.

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

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

6. ATTACHMENTS:

Facsimile labeling of the package insert is attached to this document.