

Date of Approval: February 27, 2004

FREEDOM OF INFORMATION SUMMARY

NADA 140-338

NAXCEL Sterile Powder

Ceftiofur sodium

This supplement updates survey microbiological data and adds NCCLS interpretive criteria for equine isolates to the NAXCEL Sterile Powder package insert

Sponsored by:

Pharmacia & Upjohn Co.

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1. GENERAL INFORMATION:

- a. File Number: NADA 140-338
- b. Sponsor: Pharmacia & Upjohn Co.
7000 Portage Road
Kalamazoo, MI 49001-0199
- Drug Labeler Code: 000009
- c. Established Name: ceftiofur sodium
- d. Proprietary Name: NAXCEL Sterile Powder
- e. Dosage Form: Injectable
- f. How Supplied: 1 gram and 4 gram vials
- g. How Dispensed: Rx
- h. Amount of Active Ingredients: Each mL of reconstituted solution contains ceftiofur sodium equivalent to 50 mg ceftiofur
- i. Route of Administration: Intramuscular and subcutaneous injections
- j. Species/Class: Cattle, swine, sheep, goats, dogs, horses, day-old chickens, and day-old turkey poults
- k. Recommended Dosage: Horse: 1 to 2 mg/lb body weight IM only
(relevant to current submission)
- l. Pharmacological Category: antimicrobial
- m. Indications: **Horse:** NAXCEL Sterile Powder is indicated for the treatment of respiratory infections in horses associated with *Streptococcus zooepidemicus*.
(relevant to current submission)
- n. Effect of Supplement: This supplement updates survey microbiological data and adds the National Committee for Clinical Laboratory Standards' (NCCLS) interpretive criteria for equine isolates to the NAXCEL Sterile Powder package insert.

2. EFFECTIVENESS:

Table 2 of the package insert for NAXCEL Sterile Powder presents bacterial isolates collected over time from diagnostic laboratories in the US and Canada in tabular format. In the revised package insert, updated *in vitro* minimum inhibitory concentration (MIC) data for equine respiratory pathogens have been added to Table 2.

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	<i>Mannheimia haemolytica</i>	110	1997-1998	0.06	≤ 0.03-0.25	
	<i>Mannheimia haemolytica</i>	139	1998-1999	≤ 0.03	≤ 0.03-0.5	
	<i>Mannheimia haemolytica</i>	209	1999-2000	≤ 0.03	≤ 0.03-0.12	
	<i>Mannheimia haemolytica</i>	189	2000-2001	≤ 0.03	≤ 0.03-0.12	
	<i>Pasteurella multocida</i>	107	1997-1998	≤ 0.03	≤ 0.03-0.25	
	<i>Pasteurella multocida</i>	181	1998-1999	≤ 0.03	≤ 0.03-0.5	
	<i>Pasteurella multocida</i>	208	1999-2000	≤ 0.03	≤ 0.03-0.12	
	<i>Pasteurella multocida</i>	259	2000-2001	≤ 0.03	≤ 0.03-0.12	
	<i>Haemophilus somnus</i>	48	1997-1998	≤ 0.03	≤ 0.03-0.25	
	<i>Haemophilus somnus</i>	87	1998-1999	≤ 0.03	≤ 0.03-0.125	
	<i>Haemophilus somnus</i>	77	1999-2000	≤ 0.03	≤ 0.03-0.06	
	<i>Haemophilus somnus</i>	129	2000-2001	≤ 0.03	≤ 0.03-0.12	
	<i>Bacteroides fragilis</i> group	29	1994	16.0	≤ 0.06->16.0	
	<i>Bacteroides</i> spp., non-fragilis group	12	1994	16.0	0.13->16.0	
	<i>Peptostreptococcus anaerobius</i>	12	1994	2.0	0.13-2.0	
Swine	<i>Actinobacillus pleuropneumoniae</i>	97	1997-1998	≤ 0.03	no range	
	<i>Actinobacillus pleuropneumoniae</i>	111	1998-1999	≤ 0.03	≤ 0.03-0.25	
	<i>Actinobacillus pleuropneumoniae</i>	126	1999-2000	≤ 0.03	≤ 0.03-0.06	
	<i>Actinobacillus pleuropneumoniae</i>	89	2000-2001	≤ 0.03	≤ 0.03-0.06	
	<i>Pasteurella multocida</i>	114	1997-1998	≤ 0.03	≤ 0.03-1.0	
	<i>Pasteurella multocida</i>	147	1998-1999	≤ 0.03	≤ 0.03-0.5	
	<i>Pasteurella multocida</i>	173	1999-2000	≤ 0.03	≤ 0.03-0.06	
	<i>Pasteurella multocida</i>	186	2000-2001	≤ 0.03	≤ 0.03-0.12	
	<i>Streptococcus suis</i>	106	1997-1998	0.5	≤ 0.03-4.0	
	<i>Streptococcus suis</i>	142	1998-1999	0.25	≤ 0.03-1.0	
	<i>Streptococcus suis</i>	146	1999-2000	0.06	≤ 0.03-4.0	
	<i>Streptococcus suis</i>	167	2000-2001	0.06	≤ 0.03-4.0	
	<i>Salmonella choleraesuis</i>	96	1999-2000	1.0	0.03->4.0	
	<i>Salmonella choleraesuis</i>	101	2000-2001	1.0	0.5-2.0	
	<i>Erysipelothrix rhusiopathiae</i>	44	2002	≤ 0.03	≤ 0.03-0.06	
	Equine	<i>Streptococcus equi</i> subsp. <i>equi</i>	12	1994	≤ 0.0019	no range
		<i>Streptococcus equi</i> subsp. <i>equi</i>	29	2002	≤ 0.03	≤ 0.03-0.05
		<i>Streptococcus zooepidemicus</i>	48	1994	≤ 0.0019	no range

	<i>Streptococcus zooepidemicus</i>	59	2002	≤ 0.03	≤ 0.03-0.25
	<i>Rhodococcus equi</i>	66	1998	4.0	≤ 0.03-16.0
	<i>Rhodococcus equi</i>	42	2002	8.0	≤ 0.03->32.0
	<i>Bacteroides fragilis</i> group	32	1995	> 16.0	0.13-> 16.0
	<i>Bacteroides</i> spp., non-fragilis group	12	1995	4.0	0.25-4.0
	<i>Fusobacterium necrophorum</i>	16	1995	≤ 0.06	no range
Canine	<i>Escherichia coli</i>	26	2000	32	0.25->32
	<i>Proteus mirabilis</i>	14	2000	0.25	0.06-0.25
Turkey	<i>Escherichia coli</i>	17	1998-1999	1.0	0.25-1.0
	<i>Escherichia coli</i>	25	1999-2000	0.50	0.12-0.50
	<i>Escherichia coli</i>	20	2000-2001	2.0	0.12-16
	<i>Citrobacter</i> spp.	37	1995	32.0	0.5->32.0
	<i>Enterobacter</i> spp.	51	1995	> 32.0	0.13->32.0
	<i>Klebsiella</i> spp.	100	1995	1.0	0.13-2.0
	<i>Proteus</i> spp.	19	1995	1.0	0.06-32.0
	<i>Pseudomonas</i> spp.***	31	1995	> 32.0	0.06->32.0
	<i>Salmonella</i> spp.	24	1995	1.0	0.5-1.0
	<i>Staphylococcus</i> spp. (coagulase-positive)	17	1995	2	1.0-2.0
	<i>Staphylococcus</i> spp. (coagulase-negative)	26	1995	8	0.13->32.0
Chicken	<i>Escherichia coli</i>	62	1997-1998	0.50	0.25-2.0
	<i>Escherichia coli</i>	53	1998-1999	4.0	0.25->4
	<i>Escherichia coli</i>	67	1999-2000	0.50	0.12-16
	<i>Escherichia coli</i>	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.

***MIC₅₀ is 32 µg/mL

The interpretive criteria for equine isolates have been added to the package insert. The interpretive criteria for ceftiofur are described below Table 2 in the package insert as follows:

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	≤ 2.0	(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.

Based on the pharmacokinetic studies of ceftiofur in horses after a single intramuscular injection of 1 mg ceftiofur equivalents/lb (2.2 mg/kg) BW, clinical effectiveness data and MIC data, the following breakpoint is recommended by NCCLS.

Zone Diameter (mm)	MIC ($\mu\text{g/mL}$)	Interpretation
≥ 22	≤ 0.25	(S) Susceptible

The susceptible only category is used for populations of organisms (usually one species) for which regression analysis (disk vs. MIC) cannot be performed. These breakpoints will permit detection of strains with decreased susceptibility as compared to the original population.

3. TARGET ANIMAL SAFETY:

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

4. HUMAN SAFETY:

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

5. 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 provide updated equine clinical microbiology information and NCCLS interpretive criteria for use by veterinarians to assist them in making sound therapeutic decisions for the use of NAXCEL Sterile Powder in the horse.

The product remains restricted to use by or on the order of a licensed veterinarian because professional expertise is needed for the diagnosis and treatment of diseases in cattle, swine, sheep, goats, dogs, horses, day-old chickens, 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.

According to the Center's supplemental approval policy (21 CFR 514.106), this is a Category II change. 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.

6. ATTACHMENTS:

Facsimile labeling is attached as indicated below:

Package insert