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	*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 equi subsp. *equi*	29	2002	≤ 0.03	≤ 0.03-0.05
	Streptococcus zooepidemicus	48	1994	≤ 0.0019	no range

	Streptococcus zooepidemicus	59	2002	≤ 0.03	≤ 0.03-0.25
	Rhodococcus equi	66	1998	4.0	≤ 0.03-16.0
	Rhodococcus equi	42	2002	8.0	≤ 0.03->32.0
	Bacteroides fragilis group	32	1995	> 16.0	0.13-> 16.0
	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	1.0-2.0
	Staphylococcus spp. (coagulase-negative)	26	1995	8	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

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 (µg/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