

EXCEDETM FOR SWINE

(Ceftiofur Crystalline Free Acid)
Sterile Suspension 100 mg/mL



t_{1/2} = terminal phase biological half life (in hours)

Table 2. Ceftiofur MIC values from field studies evaluating SRD in the U.S. (1996/1997 and 2000/2001)

Pathogen	Number of isolates	MIC ₉₀ [*] (µg/mL)	MIC range (µg/mL)
<i>A. pleuropneumoniae</i>	28	≤0.03	≤0.03-0.06
<i>P. multocida</i>	58	≤0.03	≤0.03 [†]
<i>S. suis</i>	41	0.12	≤0.03-0.5
<i>H. parasuis</i> **	72	0.06	≤0.03-0.25

* MIC for 90% of the isolates.

** These MIC data were obtained using NCCLS procedures but quality control values for *H. parasuis* had not been standardized.

[†] No range, all isolates yielded the same value.

Table 3. Ceftiofur MIC values from U.S. and Canadian diagnostic laboratory survey data* (1997 to 2001)

Pathogen	Year Tested	Origin of Isolates	Number of Isolates	MIC ₉₀ ** (µg/mL)	MIC Range (µg/mL)
<i>Actinobacillus pleuropneumoniae</i>	1997-1998	U.S.	97	≤0.03	≤0.03 [†]
<i>Pasteurella multocida</i>	1997-1998	U.S.	114	≤0.03	≤0.03-1.0
<i>Streptococcus suis</i>	1997-1998	U.S.	106	0.50	≤0.03-4.0
<i>Actinobacillus pleuropneumoniae</i>	1998-1999	U.S.	111	≤0.03	≤0.03-0.25
<i>Pasteurella multocida</i>	1998-1999	U.S.	147	≤0.03	≤0.03-0.50
<i>Streptococcus suis</i>	1998-1999	U.S.	142	0.25	≤0.03-1.0
<i>Actinobacillus pleuropneumoniae</i>	2000	U.S.	126	≤0.03	≤0.03-0.06
<i>Pasteurella multocida</i>	2000	U.S.	173	≤0.03	≤0.03-0.06
<i>Streptococcus suis</i>	2000	U.S.	146	0.06	≤0.03-4.0
<i>Actinobacillus pleuropneumoniae</i>	2000-2001	U.S.	89	≤0.03	≤0.03-0.06
<i>Pasteurella multocida</i>	2000-2001	U.S.	186	≤0.03	≤0.03-0.12
<i>Streptococcus suis</i>	2000-2001	Canada	167	0.06	≤0.03-4.0

* The following *in vitro* data are available, but their clinical significance is unknown.

** MIC for 90% of the isolates.

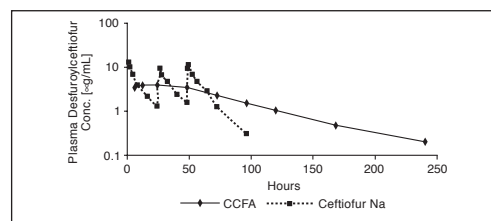
[†] No range, all isolates yielded the same value.

Table 4. Acceptable quality control ranges for ceftiofur against NCCLS recommended American Type Culture Collection (ATCC) reference strains

Organism Name (ATCC No.)	MIC (µg/mL)	Zone Diameter, mm (Disk Content 30 µg)
<i>E. coli</i> ATCC 25922	0.25-1.0	26-31
<i>S. aureus</i> ATCC 29213	0.25-1.0	—
<i>S. aureus</i> ATCC 25923	—	27-31
<i>P. aeruginosa</i> ATCC 27853	16.0-64.0	14-18

The average plasma concentrations of ceftiofur- and desfurioceftiofur-related metabolites for CCFA (EXCEDE FOR SWINE Sterile Suspension 100 mg/mL) after IM administration of 2.27 mg CE/lb (5.0 mg CE/kg) BW and those for ceftiofur sodium (NAXCEL Sterile Powder) after IM administration at 1.36 mg CE/lb (3 mg CE/kg) BW for three consecutive days are presented in Figure 2 below.

Figure 2. Average plasma concentrations of ceftiofur- and desfurioceftiofur-related metabolites for CCFA (EXCEDE FOR SWINE Sterile Suspension 100 mg/mL) after IM administration of 2.27 mg CE/lb (5.0 mg CE/kg) BW and those for ceftiofur sodium (NAXCEL Sterile Powder) after IM administration at 1.36 mg CE/lb (3 mg CE/kg) BW for three consecutive days.



Pharmacokinetic parameters measured after a single IM administration of 2.27 mg CE/lb (5.0 mg CE/kg) BW of EXCEDE FOR SWINE Sterile Suspension 100 mg/mL in the post-auricular region of the neck of swine are presented in the following table (Table 1).

MICROBIOLOGY

Ceftiofur has demonstrated *in vitro* and *in vivo* activity against *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Haemophilus parasuis* and *Streptococcus suis*, the four major pathogenic bacteria associated with SRD. Summaries of minimum inhibitory concentration (MIC) values for ceftiofur against SRD pathogens collected from two clinical field studies evaluating SRD in the U.S. (1996/97 and 2000/01) and several diagnostic laboratories in North America (1997-2001) are presented in Tables 2 and 3, respectively. Testing was conducted in accordance with National Committee for Clinical Laboratory Standards (NCCLS) procedures.¹ Quality control strains were included in each run and results were within acceptable ranges.

Based on pharmacokinetic and clinical effectiveness studies of ceftiofur in swine after a single intramuscular injection of 2.27 mg CE/lb (5.0 mg CE/kg) BW 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 the infection is in a body site where 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 procedures¹ require the use of laboratory control organisms for both standardized diffusion techniques and standardized dilution techniques. The

¹ Minimum inhibitory concentration for 90% of the isolates

30 µg ceftiofur sodium disk and the ceftiofur sodium standard reference powder (or disk) should provide MIC values and zone diameters for the reference strains as presented in Table 4. Ceftiofur sodium disks or powder forms of ceftiofur (sodium, hydrochloride and free acid).

EFFECTIVENESS

A challenge model study was conducted to evaluate the effectiveness of EXCEDE FOR SWINE Sterile Suspension 100 mg/mL and select an appropriate dose for field testing. Pigs were challenged with an intratracheal administration of *Actinobacillus pleuropneumoniae*. EXCEDE FOR SWINE Sterile Suspension 100 mg/mL was administered as a single IM dose injected in the post-auricular region of the neck. Control pigs received a placebo injection. Mortality rates and lung lesion scores were lower for the EXCEDE FOR SWINE Sterile Suspension 100 mg/mL-treated groups compared with the placebo-treated control group. A dose range of 2.27 to 3.18 mg CE/lb (5.0 to 7.0 mg CE/kg) BW was selected for further field testing.

The effectiveness of a single dose of 2.27 or 3.18 mg CE/lb BW (5.0 or 7.0 mg CE/kg BW) EXCEDE FOR SWINE Sterile Suspension 100 mg/mL for the treatment of SRD was confirmed in a well-controlled, multilocation field study. A total of 706 pigs with clinical signs of bacterial respiratory disease were enrolled and treated with a placebo injection or EXCEDE FOR SWINE Sterile Suspension 100 mg/mL administered as a single IM injection in the postauricular region of the neck. Clinical observations were performed on Days 1-7 and rectal temperatures were taken on Days 1, 3, and 6 following treatment (Day 0). Necropsies were performed on all pigs that died during the study and after euthanasia of all remaining study pigs at the end of the 14-day post-enrollment study period. Lung lesions were scored and lungs were submitted for bacterial identification. Mortality rates were numerically lower (but not statistically different) for the EXCEDE FOR SWINE Sterile Suspension 100 mg/mL treated groups (4.3% for the 5.0 mg CE/kg BW group and 4.2% for the 7.0 mg CE/kg BW group) compared with the placebo-treated control group (6.3%). There was a statistically significant (p<0.05) improvement in clinical cure rates for the EXCEDE FOR SWINE Sterile Suspension 100 mg/mL-treated groups (24.8% for the 5.0 mg CE/kg BW group and 26.4% for the 7.0 mg CE/kg BW group) compared with the placebo-treated control group (17.7%). Lung lesion scores were numerically higher (but not statistically different) for the EXCEDE FOR SWINE Sterile Suspension 100 mg/mL-treated groups (10.4% for both the 5.0 mg CE/kg BW and the 7.0 mg CE/kg BW group) compared with the placebo-treated control group (9.2%). Bacteriological culture of the lungs of study pigs identified the following ceftiofur-susceptible respiratory pathogens: *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Haemophilus parasuis*, and *Streptococcus suis*.

ANIMAL SAFETY

After parental administration, CCFA, ceftiofur sodium, and ceftiofur hydrochloride are metabolized to the same principal metabolite, desfurioceftiofur. Plasma levels achieved are similar after recommended dosing (Figure 2). Therefore, studies conducted with ceftiofur sodium are adequate to evaluate the systemic safety of CCFA. Results from a five-day tolerance study in normal feeder pigs indicated that ceftiofur sodium produced no overt adverse signs of toxicity and was well tolerated when administered at 57 mg CE/lb (125 mg/kg) BW (more than 25 times the recommended dosage of CCFA) for five consecutive days. An additional dose toxicity study was conducted to determine the safety margin of ceftiofur in swine. Five barrows and five gilts per group were administered ceftiofur sodium IM at 0, 2.27, 6.81 and 11.36 mg CE/lb (0, 5, 15, 25 mg CE/kg) BW (0, 1, 3 and 5 times the recommended dosage for CCFA) for 15 consecutive days. There were no adverse systemic effects observed, indicating that ceftiofur sodium has a wide margin of safety when administered intramuscularly in feeder pigs.

A separate study evaluated the injection site tissue tolerance of EXCEDE FOR SWINE Sterile Suspension 100 mg/mL in swine when administered intramuscularly as a single injection at the maximum recommended dose volume of 2 mL (approximately 5 mg CE/kg BW) per injection site. Because injection site volumes greater than 2 mL may result in violative residues, only injection volumes of 2 mL were evaluated in this study. EXCEDE FOR SWINE Sterile Suspension 100 mg/mL was injected intramuscularly into each side of the neck of six swine at a dose volume of 2 mL/injection site. Clinical observations were made daily. At 3, 7 and 10 days post-injection, pairs of injection sites were dissected for pathological examination (4 injection sites per time point). The injections were well tolerated in all pigs. Clinically, injection site reactions ranged from nondetectable (6 of 12 sites) to a transitory (up to 4 days post-injection) palpable, nonvisible swelling (2 of 12 sites) or a small, visible, reddened nodule at the needle insertion point (4 of 12 sites); 3 of 4 nodules were barely detectable by 3 to 7 days post-injection. There was no clinical evidence of the injections at 10 days postinjection. At necropsy, half of the injection sites at both 3 and 7 days post-injection were scored as "negative" for irritation and the other half were scored as "slight irritation". One animal had a visible lesion described as an area of tan with red speckles present in the deep muscle fascia, less than 6 cm², at 10 days post-injection; this lesion and the remaining injection sites evaluated at 10 days post-injection were scored as "negative" for irritation.

STORAGE CONDITIONS

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP]. Shake well before using. Contents should be used within 12 weeks after the first dose is removed.

HOW SUPPLIED

EXCEDE FOR SWINE Sterile Suspension 100 mg/mL is available in the following package size:

100 mL vial NDC 0009-5223-01

¹ National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals; Approved Standard. NCCLS Document M31-A (ISBN 1-56238-377-9). NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1832, 1999.

U.S. Patent No. 5,721,359 and other patents pending.

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For intramuscular administration in the post-auricular region of the neck of swine.

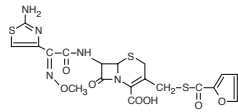
CAUTION

Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

EXCEDE FOR SWINE Sterile Suspension 100 mg/mL is a ready-to-use formulation that contains the crystalline free acid of ceftiofur, which is a broad spectrum cephalosporin antibiotic active against gram-positive and gram-negative bacteria including β-lactamase-producing strains. Like other cephalosporins, ceftiofur is bactericidal *in vitro*, resulting from inhibition of cell wall synthesis. Each mL of this ready-to-use sterile suspension contains ceftiofur crystalline free acid equivalent to 100 mg ceftiofur, in a Miglyol[®] and cottonseed oil based suspension.

Figure 1. Structure of ceftiofur crystalline free acid:



Chemical name of ceftiofur crystalline free acid:

7-[(2-(2-Amino-4-thiazolyl)-2-(methoxyimino)acetyl)amino]-3-[[[2-(furanlyl-carbonyl)thio]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene 2-carboxylic acid

EXCEDE FOR SWINE Sterile Suspension 100 mg/mL is indicated for the treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Haemophilus parasuis*, and *Streptococcus suis*.

DOSAGE

Administer by intramuscular (IM) injection in the post-auricular region of the neck as a single dosage of 2.27 mg ceftiofur equivalents (CE)/lb (5.0 mg CE/kg) body weight (BW). This is equivalent to 1 mL sterile suspension per 44 lb (20 kg) BW. No more than 2 mL should be injected in a single injection site. Injection volumes in excess of 2 mL may result in violative residues. Pigs heavier than 88 lb (40 kg) will require more than one injection.

Most animals will respond to treatment within three to five days. If no improvement is observed, the diagnosis should be reevaluated.

ADMINISTRATION

Shake well before using. EXCEDE FOR SWINE Sterile Suspension 100 mg/mL is to be administered by intramuscular injection in the post-auricular region of the neck.

CONTRAINDICATIONS

As with all drugs, the use of EXCEDE FOR SWINE Sterile Suspension 100 mg/mL is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS

FOR USE IN ANIMALS ONLY.
NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.
Restricted Drug (California) —
Use Only as Directed

Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposures to such antimicrobials, including ceftiofur, may elicit mild to severe allergic reactions in some individuals. Repeated or prolonged exposure may lead to sensitization. Avoid direct contact of the product with the skin, eyes, mouth and clothing. Sensitization of the skin may be avoided by wearing latex gloves. Persons with a known hypersensitivity to penicillin or cephalosporins should avoid exposure to this product.

In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g., skin rash, hives, difficult breathing), seek medical attention.

The material safety data sheet contains more detailed occupational safety information. To obtain a material safety data sheet (MSDS), please call 1-800-733-5500. To report any adverse events, please call 1-800-366-5288.

RESIDUE WARNINGS

- A maximum of 2 mL of formulation should be injected at each injection site. Injection volumes in excess of 2 mL may result in violative residues.
- Following label use as a single treatment, a 14-day pre-slaughter withdrawal period is required.
- Use of dosages in excess of 5.0 mg ceftiofur equivalents (CE)/kg or administration by an unapproved route may result in illegal residues in edible tissues.

PRECAUTIONS

The safety of ceftiofur has not been demonstrated for pregnant swine or swine intended for breeding.

Administration of EXCEDE FOR SWINE Sterile Suspension 100 mg/mL as directed may induce a transient reaction at the site of injection and underlying tissues that may result in trim loss of edible tissue at slaughter.

ADVERSE REACTIONS

An injection site tolerance study demonstrated that EXCEDE FOR SWINE Sterile Suspension 100 mg/mL is well tolerated in pigs. Half of the injection sites at both 3 and 7 days post-injection were scored as "negative" for irritation and the other half were scored as "slight irritation". All gross observations and measurements of injection sites qualified the sites at 10 days post-injection as "negative" for irritation. No adverse effects were observed in multi-location field efficacy studies involving more than 1000 pigs.

CLINICAL PHARMACOLOGY

Ceftiofur administered as either ceftiofur sodium (NAXCEL[®] Sterile Powder), ceftiofur hydrochloride (EXCENEL[®] RTU Sterile Suspension) or ceftiofur crystalline free acid (EXCEDE FOR SWINE Sterile Suspension 100 mg/mL) is metabolized rapidly to desfurioceftiofur, the primary metabolite. Administration of ceftiofur to swine as ceftiofur crystalline free acid (CCFA) at a single IM dosage of 2.27 mg CE/lb (5.0 mg CE/kg) BW provides concentrations of ceftiofur and desfurioceftiofur-related metabolites in plasma that are multiples above the MIC₉₀^{*} for the SRD label pathogens *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Haemophilus parasuis* and *Streptococcus suis* for an extended period of time (see Figure 2 and Tables 1-3).

Table 1. Pharmacokinetic parameters in swine after a single IM administration of EXCEDE FOR SWINE Sterile Suspension 100 mg/mL at 2.27 mg CE/lb (5.0 mg CE/kg) BW

Pharmacokinetic Parameter	Mean Value ± Standard Deviation (noncompartmental analyses)
C _{max} (µg/mL)	4.17 ± 0.92
t _{max} (h)	22.0 ± 12.2
AUC ₀₋₁₀₀ (µg·h/mL)	373.0 ± 56.1
t _{1/2} (h)	49.6 ± 11.8

C_{max} = maximum plasma concentration (in µg CE/mL)

t_{max} = the time after injection when C_{max} occurs (in hours)

AUC₀₋₁₀₀ = the area under the plasma concentration vs. time curve from time of injection to the limit of quantitation of the assay (0.15 µg CE/mL)