CHOOSE THE ONLY ANTI-INFECTIVES BACKED BY THE RESIDUE FREE GUARANTEE.

PRODUCT	ACTIVE INGREDIENT	INDICATIONS	APPROVED DOSAGE	LABELED TREATMENT AND ROUTE OF ADMINISTRATION†	MEAT WITHDRAWAL	MILK DISCARD
EXCEDE®	Ceftiofur crystalline free acid	Treatment of acute metritis, BRD†† and foot rot, and control of BRD†† in heifers	1.5 mL/100 lbs. (6.6 mg CE/kg)	**Acute postpartum metritis:** 2 doses, administered 72 hours apart Route of administration: Base of opposite ears **BRD and foot rot:** 1 dose only Route of administration: Base of ear	13 days	0 days
EXCENEL® RTU EZ	Ceftiofur hydrochloride	Treatment of acute metritis, BRD†† and foot rot	Acute metritis: 2 mL/100 lbs. BRD and foot rot: 1-2 mL/100 lbs.	**Acute postpartum metritis:** Once daily for 5 consecutive days **BRD and foot rot:** 3-5 consecutive days Route of administration: Sub-Q or IM†††	4 days	0 days
NAXCEL®	Ceftiofur sodium	Treatment of BRD†† and foot rot	1-2 mL/100 lbs. (0.5-1.0 mg/lb.)	Once daily for 3-5 consecutive days Route of administration: Sub-Q or IM†††	4 days	0 days
Polyflex®	Ampicillin	Bacterial pneumonia	2-5 mg/lb.	Once daily for 3-7 consecutive days Route of administration: IM†††	6 days	48 hours
Penicillin	Penicillin G procaine	Bacterial pneumonia	1 mL/100 lbs. (300,000 units/mL)	Once daily for up to 4 consecutive days Route of administration: IM†††	10 days	48 hours
Tetracycline	Oxytetracycline 200	Pneumonia, shipping fever, foot rot, pinkeye, scours, wooden tongue, *Leptospira* pomona	3-5 mL/100 lbs. (9 mg/lb.)	Once daily for up to 4 consecutive days Route of administration: IV†††	28 days	96 hours

*Based on label indications
**BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni*
***Route of administration: IM=Intramuscular
Sub-Q=Subcutaneous
IV=Intravenous

You have our unwavering support.

Zoetis is committed to you, the health and profitability of your dairy operation, and the quality and safety of the food you produce. In fact, no other animal health company stands behind its products with this kind of promise.

OUR GUARANTEE: NO MILK OR MEAT RESIDUES.

You won't have to worry about a violative residue for ceftiofur in milk or meat when you use any of these anti-infectives from Zoetis:

- EXCENEL® RTU EZ (*ceftiofur hydrochloride*) Sterile Suspension
- EXCEDE® (*ceftiofur crystalline free acid*) Sterile Suspension
- NAXCEL® (*ceftiofur sodium*) Sterile Powder

That's because only Zoetis offers the Residue Free Guarantee™.* When you use these products according to label indications,** you have our assurance that you will not have a violative milk or meat residue for ceftiofur. If a violative residue occurs from on-label use, Zoetis will compensate you for the beef market value of the animal, or purchase the tanker of milk. It's that simple.

For more details on the Residue Free Guarantee, visit www.AvoidResidues.com, consult your veterinarian or Zoetis representative, or call 888-ZOETIS1 (888-963-8471).

**Excludes off-label use prescribed by a veterinarian.

EXCEDE® (Ceftiofur Crystalline Free Acid) Sterile Suspension

EXCENEL® RTU EZ (ceftiofur hydrochloride) Sterile Suspension

NAXCEL® (ceftiofur sodium) Sterile Powder

Important Safety Information for EXCEDE: The use of EXCEDE is contraindicated in animals with known allergy to ceftiofur or to the ß-lactam group (penicillins and cephalosporins) of antimicrobials. Though safe in cattle when properly administered, inadvertent intra-arterial injection is possible and fatal. EXCEDE has a pre-slaughter withdrawal time of 13 days following the last dose in cattle. Do not use in calves to be processed for veal.

Important Safety Information for EXCENEL RTU EZ: EXCENEL RTU EZ should not be used in animals found to be hypersensitive to the product. EXCENEL RTU EZ has a pre-slaughter withdrawal period of four days following the last dose.

Important Safety Information for NAXCEL: NAXCEL should not be used in animals found to be hypersensitive to the product. NAXCEL has a pre-slaughter withdrawal time of four days.

Effective. On-label. No risk of meat or milk residues. We guarantee it.

DAIRY WELLNESS MAKES A DIFFERENCE™

zoetis™

*__Residue Free Guarantee:__ If you use a Zoetis-branded ceftiofur product according to label indications, and experience a violative ceftiofur milk or meat residue, Zoetis will compensate you for the beef market value of the animal or purchase the tanker of milk at fair market value. You must purchase the product from a Zoetis-approved supplier, use the product according to label indications, have documentation of the product purchase and treatment records, and have conducted training on appropriate use to ensure proper dose and route of administration of the product. Extra-label use as prescribed by a veterinarian is excluded from the guarantee. If you experience a ceftiofur residue violation after following label indications and the above steps, contact Zoetis VMIPS (Veterinary Medical Information and Product Support) at 888-ZOETIS1 (888-963-8471) to report the situation.

EXCEDE®
(Ceftiofur Crystalline Free Acid)
Sterile Suspension

For subcutaneous injection in the posterior aspect of the ear where it attaches to the head (base of the ear) in lactating dairy cattle. For subcutaneous injection in the middle third of the posterior aspect of the ear or in the posterior aspect of the ear where it attaches to the head (base of the ear) in beef and non-lactating dairy cattle. Not for use in calves to be processed for veal.

CAUTION

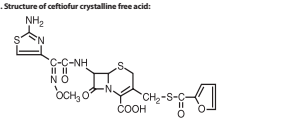
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

EXCEDE Sterile Suspension 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 ß-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 200 mg ceftiofur, in a caprylic/capric triglyceride (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-furanylcarbonyl)thio] methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene 2-carboxylic acid

INDICATIONS

EXCEDE Sterile Suspension is indicated for treatment of bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia haemolytica, Pasteurella multocida*, and *Histophilus somni* in beef, non-lactating dairy, and lactating dairy cattle.

EXCEDE Sterile Suspension is also indicated for the control of respiratory disease in beef and non-lactating dairy cattle which are at high risk of developing BRD associated with *M. haemolytica, P. multocida*, and *H. somni*.

EXCEDE Sterile Suspension is also indicated for the treatment of bovine foot rot (interdigital necrobacillosis) associated with *Fusobacterium necrophorum* and *Porphyromonas levii* in beef, non-lactating dairy, and lactating dairy cattle.

EXCEDE Sterile Suspension is also indicated for treatment of acute metritis (0-10 days post-partum) associated with bacterial organisms susceptible to ceftiofur in lactating dairy cattle.

DOSAGE

Treatment of BRD and bovine foot rot

Administer as a single subcutaneous injection in the posterior aspect of the ear where it attaches to the head (base of the ear) to cattle at a dosage of 3.0 mg ceftiofur equivalents (CE)/lb (6.6 mg CE/kg) body weight (BW) (1.5 mL sterile suspension per 100 lb BW).

In beef and non-lactating dairy cattle, EXCEDE Sterile Suspension may also be administered as a single subcutaneous injection in the middle third of the posterior aspect of the ear at a dosage of 3.0 mg CE/lb (6.6 mg CE/kg) BW (1.5 mL sterile suspension per 100 lb BW).

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

Control of BRD

Administer as a subcutaneous injection either in the middle third of the posterior aspect of the ear or in the posterior aspect of the ear where it attaches to the head (base of the ear) to beef and non-lactating dairy cattle at a dosage of 3.0 mg CE/lb (6.6 mg CE/kg) BW (1.5 mL sterile suspension per 100 lb BW).

Clinical studies indicate that administration of EXCEDE Sterile Suspension is effective for the control of respiratory disease in beef and non-lactating dairy cattle at "high risk" of developing BRD. One or more of the following factors typically characterizes calves on arrival at high risk of developing BRD.

- Cattle are from multiple farm origins,
- cattle have had extended transport times (that may have included few if any rest stops),
- ambient temperature change from origin to arrival of 30° F or more,
- cattle have had continued exposure to extremely wet or cold weather conditions,
- cattle have experienced excessive shrink or excessive arrival processing procedures (such as castration, dehorning).

Treatment of Acute Metritis

Administer as a subcutaneous injection in the posterior aspect of the ear where it attaches to the head (base of the ear) to lactating dairy cattle at a dosage of 3.0 mg CE/lb (6.6 mg CE/kg) BW (1.5 mL sterile suspension per 100 lb BW). Repeat this dose in the contra-lateral (opposite) ear approximately 72 hours following the initial dose.

Table 1. Dosing Schedule for EXCEDE Sterile Suspension.

Weight (lb)	Dose Volume (mL)
100	1.5
200	3.0
300	4.5
400	6.0
500	7.5
600	9.0
700	10.5
800	12.0
900	13.5
1000	15.0

Weight (lb)	Dose Volume (mL)
1100	16.5
1200	18.0
1300	19.5
1400	21.0
1500	22.5
1600	24.0
1700	25.5
1800	27.0
1900	28.5
2000	30.0

ADMINISTRATION

ADMINISTRATION FOR THE MIDDLE THIRD OF THE EAR

- **Shake well before using.** Please read the complete package insert before administering EXCEDE Sterile Suspension subcutaneously in the posterior ear of cattle.
- Deposit as a single subcutaneous injection in the middle third of the posterior aspect of the ear, avoiding all blood vessels. See Figures 2 and 3.
- Adjust the needle insertion point to avoid any blood vessels, previous implants, ear tags or ear tag holes. Do not administer intra-arterially.
- Deliver the entire contents of the syringe.
- When administered correctly, a subcutaneous bleb of EXCEDE Sterile Suspension will appear.
- When withdrawing the needle, apply pressure to the needle insertion point, and massage toward the base of the ear.

ADMINISTRATION FOR BASE OF THE EAR

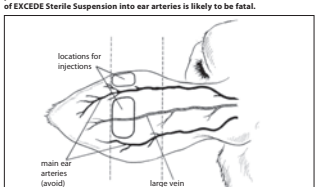
In lactating dairy cattle the injection techniques for subcutaneous (SC) injection in the posterior aspect of the ear where it attaches to the head (base of the ear) can be made by the rostral or ventral injection techniques.

In beef and non-lactating dairy cattle the SC injection in the base of the ear can be made by the rostral, ventral or toward the opposite eye injection techniques.

- **Shake well before using.** Please read the complete package insert before administering EXCEDE Sterile Suspension subcutaneously in the posterior aspect of the ear where it attaches to the head (base of the ear).
- The subcutaneous (SC) injection may be made using the toward the opposite eye, rostral, or ventral techniques. Hold the syringe and needle and insert the needle as described below.
- Deliver the entire contents of the syringe.
- Do not administer EXCEDE Sterile Suspension in the neck.

Figure 2. Subcutaneous administration of EXCEDE Sterile Suspension in the middle third of the posterior aspect of the ear.

Figure 3. Diagram of the approximate locations of the major arteries of the posterior ear and the recommended needle insertion locations. Administration of EXCEDE Sterile Suspension into ear arteries is likely to be fatal.



Administration for the Base of the Ear: Toward the Opposite Eye Technique

- Hold the syringe and needle behind the ear to be dosed so the needle and syringe point in the direction of an imaginary line that would pass through the head toward the animal's opposite eye. See Figures 4 and 5.
- Insert the needle through the loose skin in the posterior aspect of the ear where it attaches to the head (base of the ear) while maintaining this angle. See Figure 4.

Figure 4. Subcutaneous administration of EXCEDE Sterile Suspension in the posterior aspect of the ear where it attaches to the head (base of the ear).

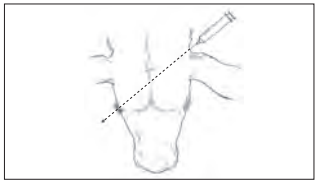
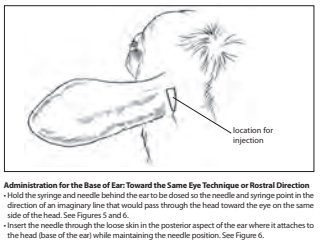


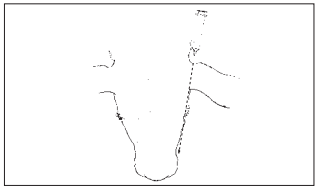
Figure 5. Injection location for the subcutaneous administration of EXCEDE Sterile Suspension in the posterior aspect of the ear where it attaches to the head (base of the ear).



Administration for the Base of Ear: Toward the Same Eye Technique or Rostral Direction

- Hold the syringe and needle behind the ear to be dosed so the needle and syringe point in the direction of an imaginary line that would pass through the head toward the eye on the same side of the head. See Figures 5 and 6.
- Insert the needle through the loose skin in the posterior aspect of the ear where it attaches to the head (base of the ear) while maintaining the needle position. See Figure 6.

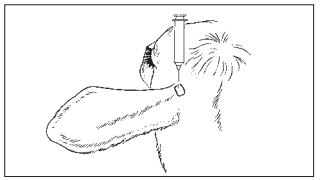
Figure 6. Diagram of head showing the direction for the base of ear injections administered rostrally toward the eye on the same side of the head into the loose skin in the caudal aspect of the base of the ear.



Administration for Base of the Ear: Ventral Technique

- Hold the syringe and needle above the ear to be dosed so that the needle and syringe are pointing ventrally toward the base of the ear. The needle will be inserted into the loose skin in the posterior aspect of the ear where it attaches to the head (base of the ear) while pointing ventrally. Care should be taken to not insert the needle through the cartilage of the ear. See Figure 7.
- Insert the needle through the loose skin in the posterior aspect of the ear where it attaches to the head (base of the ear) while maintaining needle position. See Figure 7.

Figure 7. Diagram of head showing the direction of base of ear injections when administered ventrally into the loose skin in the caudal aspect of the base of the ear.



CONTRAINDICATIONS

As with all drugs, the use of EXCEDE Sterile Suspension 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.

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 protective 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 please call 1-800-733-5500. To report any adverse event please call 1-800-366-5288.

Intra-arterial injection may occur during administration of EXCEDE Sterile Suspension via middle third of the ear injection or base of the ear injection directed toward the opposite eye. Intra-arterial injection of EXCEDE Sterile Suspension is likely to result in sudden death of the animal.

RESIDUE WARNINGS

- **Following label use as either a single-dose or 2-dose regimen, a 13-day pre-slaughter withdrawal period is required after the last treatment.**
- **Following label use as either a single-dose or 2-dose regimen, no milk discard period is required for this product.**
- **Use of dosages in excess of 3.0 mg CE/lb. (6.6 mg CE/kg) BW or administration by unapproved routes (subcutaneous injection in the neck or intramuscular injection) may cause violative residues.**
- **A withdrawal period has not been established for this product in pre-ruminating calves.**
- **Do not use in calves to be processed for veal.**

ANTIBACTERIAL WARNINGS

Use of antibacterial drugs in the absence of a susceptible bacterial infection is unlikely to provide benefit to treated animals and may increase the risk of the development of drug-resistant bacteria.

PRECAUTIONS

Following subcutaneous injection in the middle third of the posterior aspect of the ear, thickening and swelling (characterized by aseptic cellular infiltrate) of the ear may occur. As with other parenteral injections, localized post-injection bacterial infections may result in abscess formation. Attention to hygienic procedures can minimize their occurrence.

Following injection in the posterior aspect of the ear when it attaches to the head (base of the ear), areas of discoloration and signs of inflammation may persist at least 13 days post administration resulting in trim loss of edible tissue at slaughter. Injection of volumes greater than 20 mL, in the middle third of the ear, may result in open draining lesions in a small percentage of cattle.

The effects of ceftiofur on bovine reproductive performance, pregnancy, and lactation have not been determined.

ADVERSE EFFECTS

Intra-arterial injection may occur during administration of EXCEDE Sterile Suspension via middle third of the ear injection or base of the ear injection directed toward the opposite eye. Intra-arterial injection of EXCEDE Sterile Suspension is likely to result in sudden death of the animal. During the conduct of clinical studies, there was a low incidence of acute death (see ANIMAL SAFETY) confirmed to be the result of inadvertent intra-arterial injection. No other adverse systemic effects were noted for either the antibiotic or formulation during any of the clinical and target animal safety studies.

CLINICAL PHARMACOLOGY

Ceftiofur administered as either ceftiofur sodium (NAXCEL® Sterile Powder), ceftiofur hydrochloride (EXCENEL® RTU Sterile Suspension), or ceftiofur crystalline free acid (EXCEDE Sterile Suspension) is metabolized rapidly to desfuroylceftiofur, the primary metabolite. Subcutaneous administration of ceftiofur crystalline free acid, either in the middle third of the posterior aspect of the ear (middle third of the ear, MOE) of beef and non-lactating dairy cattle, or in the posterior aspect of the ear where it attaches to the head (base of the ear, BOE) of beef, non-lactating dairy, and lactating dairy cattle, provides therapeutic concentrations of ceftiofur and desfuroylceftiofur-related metabolites in plasma above the lowest minimum inhibitory concentration to encompass 90% of the most susceptible isolates (MIC_{90}) for the labeled BRD pathogens, *Pasteurella multocida, Mannheimia haemolytica* and *Histophilus somni*, for generally not less than 150 hours after a single administration (See Figure 8).

Single Dose Regimen

The pharmacokinetic parameters for the two subcutaneous locations of injection (MOE and BOE) are found in Table 2. Statistical analyses of the data from these two subcutaneous injection sites (MOE and BOE) demonstrate that they are therapeutically equivalent.

Figure 8. Average (n=12/group) plasma concentrations of ceftiofur and desfuroylceftiofur-related metabolites after administration of EXCEDE Sterile Suspension at 3.0 mg CE/lb (6.6 mg CE/kg) BW via subcutaneous injection into one of two different locations of the ear, middle third of the ear (MOE Cattle) and base of the ear (BOE Cattle) in beef cattle as well into the base of the ear (BOE Lactating) in lactating dairy cattle.

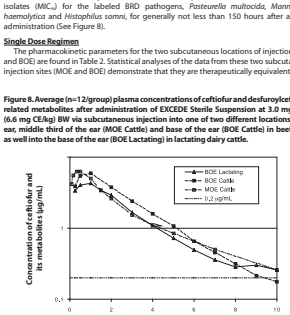


Table 2. Average (n = 12/group) pharmacokinetic parameters for ceftiofur and desfuroylceftiofur metabolites calculated after a single subcutaneous administration of 3.0 mg CE/lb (6.6 mg CE/kg) BW of EXCEDE Sterile Suspension in either the middle third of the ear or the base of the ear.

Pharmacokinetic Parameter	Beef - Middle Third of the Ear Mean Value ± Standard Deviation	Beef - Base of the Ear Mean Value ± Standard Deviation	Dairy Cow - Base of the Ear Mean Value ± Standard Deviation
C_{max} (µg CE/mL)	6.90 ± 2.68	6.39 ± 1.79	4.44 ± 1.65
t_{max} (h)	12.0 ± 6.2	19.8 ± 5.81	19.00 ± 8.02
$AUC_{0\text{-}inf}$ (µg-h/mL)	376 ± 66.1	412 ± 67.3	313 ± 85.5
$t_{1/2,\lambda\,middle}$ (h)	183 ± 40.8	NE	NE
$t_{1/2,\lambda\,base}$ (h)	246 ± 48.5	218 ± 45.5	205 ± 35.7
$t_{1/2}$ (h)	62.3 ± 13.5	40.7 ± 11.2	43.92 ± 9.84

C_{max} (µg CE/mL) = maximum plasma concentration (in µg CE/mL).
t_{max} (h) = the time after injection when C_{max} occurs (in hours).
$AUC_{0\text{-}inf}$ (µg-h/mL) = 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).
$t_{1/2,\lambda\,middle}$ (h) = the time plasma concentrations remain above 0.2 µg CE/mL (in hours), estimated using compartmental pharmacokinetic techniques.
$t_{1/2,\lambda\,base}$ (h) = the time plasma concentrations remain above 0.2 µg CE/mL (in hours), estimated using noncompartmental pharmacokinetic techniques.
$t_{1/2}$ (h) = terminal phase biological half life (in hours)
NE = Not estimated

Two-Dose Regimen

A two-dose regimen of 6.6 mg CE/kg BW administered 72 hours apart is required for the treatment of acute metritis in lactating cows. The mean plasma concentration vs. time profile for ceftiofur and desfuroylceftiofur-related metabolites for the 2-dose regimen in 12 cows is shown in Figure 9 below. The pharmacokinetic parameters for the 2-dose regimen are provided in Table 3.

Figure 9. LS-Mean DCA Plasma Concentration Time Profile Following Two Subcutaneous Injections of EXCEDE 72 hours apart at a Dose of 3.0 mg CE/lb (6.6 mg CE/kg) BW in 12 lactating cows.

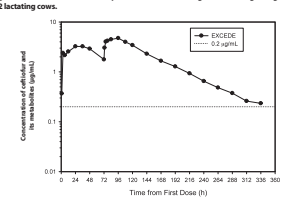


Table 3. Average (n = 12) Pharmacokinetic Parameters Following Two Subcutaneous Injections of EXCEDE Sterile Suspension at a Dose 3.0 mg CE/lb (6.6 mg CE/kg) BW at a 72 Hour Interval.

PK Parameter	Mean ± Standard Deviation
$AUC_{0\text{-}last}$ (µg-h/mL)	651 ± 119
$t_{1/2}$ (h)	55.7 ± 4.84
$t_{>0.2}$ (h)	341 ± 34.0
T_{max} (h)	77.1 ± 33.4
C_{max} (µg/mL)	5.98 ± 2.51

MICROBIOLOGY

Ceftiofur has demonstrated *in vitro* activity against *Mannheimia haemolytica, Pasteurella multocida*, and *Histophilus somni*, three major pathogens associated with BRD, and against *Fusobacterium necrophorum* and *Porphyromonas levii* associated with bovine foot rot.

A summary of the susceptibility of BRD and foot rot pathogens is presented in Table 4. BRD isolates were obtained from cattle enrolled in a field study conducted in the United States that were diagnosed with BRD. Foot rot isolates were obtained from cattle enrolled in a field study conducted in the United States and Canada that were diagnosed with foot rot. Susceptibility testing was conducted according to the Clinical and Laboratory Standards Institute (CLSI) M7-A3 and M11-A6 standards for BRD and foot rot isolates, respectively.

Table 4. Ceftiofur minimum inhibitory concentration (MIC) values* of indicated pathogens isolated from cattle with naturally occurring BRD or foot rot.

Indicated pathogen	Year of isolation	Number of isolates	MIC_{50}** (µg/mL)	MIC_{90}** (µg/mL)	MIC range (µg/mL)
Mannheimia haemolytica	1996 to 1997	75	0.008	0.015	0.001 to 0.015
Pasteurella multocida	1996 to 1997	43	0.004	0.004	0.001 to 0.015
Histophilus somni	1996 to 1997	11	0.004	0.004	0.002 to 0.015
Fusobacterium necrophorum	2006 to 2007	148	≤ 0.25	0.5	≤ 0.25 to >128
Porphyromonas levii	2006 to 2007	141	≤ 0.25	2.0	≤ 0.25 to 16

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

Based on pharmacokinetic and clinical effectiveness studies of ceftiofur in cattle after a single administration of 3.0 mg CE/lb (6.6 mg CE/kg) BW and the MIC and susceptibility data, the following breakpoints are recommended for BRD pathogens by CLSI.

Table 5. CLSI-accepted interpretive criteria* for ceftiofur against cattle respiratory pathogens.

Pathogen	Disk potency	Zone diameter (mm)			MIC breakpoint (µg/mL)		
		S	I	R	S	I	R
Mannheimia haemolytica *Pasteurella multocida* *Histophilus somni*	30 µg	≥ 21	18 to 20	≤ 17	≤ 2.0	4.0	≥ 8.0
S – Susceptible I – Intermediate R – Resistant							

* These interpretive criteria are only intended for use when CLSI M31-A2 performance standards are used to determine antimicrobial susceptibility. Interpretive criteria for bovine foot rot pathogens have not been established.

EFFECTIVENESS

A field dose confirmation study for the treatment of BRD evaluated the effectiveness of single doses of 2.0 and 3.0 mg CE/lb (4.4 or 6.6 mg CE/kg) BW for the treatment of the bacterial component of BRD under field conditions. All treatments were administered subcutaneously in the middle third of the posterior aspect of the ear. Cattle were clinically evaluated on Days 2 to 4, 14 and 28 and were observed on all other study days. The 3.0 mg CE/lb (6.6 mg CE/kg) BW EXCEDE Sterile Suspension dose significantly ($p \leq 0.05$) increased Day 14 treatment success rate, defined as animals that did not require any ancillary treatment and had a rectal temperature of <104°F, normal respiration index, and had no or mild depression on that day.

The effectiveness of a single dose of EXCEDE Sterile Suspension for the control of BRD in feedlot cattle was evaluated in a nine-location field effectiveness study. In addition to standard processing on arrival at feedlots, cattle (n=3911) considered to be at high risk for BRD were assigned to one of four arrival treatments, including EXCEDE Sterile Suspension at 2.0 or 3.0 mg CE/lb (4.4 or 6.6 mg CE/kg) BW or negative control. Effectiveness evaluation was based on the incidence of clinical BRD within 28 days following arrival processing. Administration of a single dose of EXCEDE Sterile Suspension administered subcutaneously in the middle third of the posterior aspect of the ear at arrival processing significantly reduced the incidence of BRD in high-risk feedlot cattle in the 28-day period after arrival processing compared to negative controls.

Base of the ear administration (beef and non-lactating dairy cattle) and middle third of the ear administration (lactating dairy cattle) were compared to the middle third of the ear pharmacokinetic data for beef and non-lactating dairy cattle and were found to be therapeutically equivalent.

The effectiveness of EXCEDE Sterile Suspension for the treatment of bovine foot rot was evaluated in a six-location field effectiveness study. Cattle diagnosed with bovine foot rot were enrolled and treated with EXCEDE Sterile Suspension, administered by subcutaneous injection in the base of the ear as a single dose of 3.0 mg CE/lb (6.6 mg CE/kg) dBW or an equivalent volume of a vehicle control. Cattle were clinically evaluated 7 days post-treatment for treatment success, which was based on defined decreases in lesion, swelling and lameness scores. A total of 169 beef and dairy cattle were included in the analysis. There was a statistically significant difference ($p = 0.0054$) in treatment success for EXCEDE-treated cattle (58.4%) compared to vehicle-treated control cattle (13.2%).

The effectiveness of EXCEDE Sterile Suspension for the treatment of acute metritis was evaluated in a 15-location field effectiveness study. A total of 1023 cows with a fetid vaginal discharge and a rectal temperature of ≥ 103 °F were enrolled in the study and treated with either a two-dose regimen of EXCEDE (6.6 mg CE/BW) or an equivalent volume of vehicle control, administered approximately 72 hours apart at the base of opposite ears. At 14 days post-treatment, each cow remaining in the study was examined and rectal temperature and vaginal discharge score were recorded. Cows with a non-fetid discharge, and a rectal temperature < 103 °F, and that did not require alternate ("escape") therapy during the 14_day observation period were classified as a cure. The cure rate was significantly higher ($p < 0.0001$) in EXCEDE-treated cows (362/493, 74.3%) than in vehicle-treated cows (271/489, 55.3%). One cow died 15 to 20 minutes after the second administration of EXCEDE. Necropsy findings determined the probable cause of death to be intra-arterial injection.

ANIMAL SAFETY

Systemic Safety Studies

After parenteral administration, ceftiofur crystalline free acid (as EXCEDE Sterile Suspension), ceftiofur sodium and ceftiofur hydrochloride are rapidly metabolized to desfuroylceftiofur. Therefore, studies conducted with ceftiofur sodium are adequate to evaluate the systemic safety of EXCEDE Sterile Suspension. Results from a five-day tolerance study conducted with ceftiofur sodium in normal feeder calves indicated that ceftiofur was well tolerated at 25 mg CE/lb/day for five consecutive days, approx-imately 8 times the approved dose of EXCEDE Sterile Suspension 3.0 mg CE/lb (6.6 mg CE/kg) BW. Ceftiofur administered parenterally had no adverse systemic effects.

In a 15-day safety/toxicity study, five steer and five heifer calves per group were administered ceftiofur sodium intramuscularly at 0 (vehicle control), 1, 3, 5 or 10 mg CE/lb/day thus, evaluating up to 3.3 times the approved dose of EXCEDE Sterile Suspension of 3.0 mg CE/lb/day (6.6 mg CE/kg) BW. There were no adverse systemic effects, indicating that ceftiofur has a wide margin of safety when injected intramuscularly into feeder calves. Local tissue tolerance to subcutaneous injection of EXCEDE Sterile Suspension in the posterior ear of cattle was evaluated in a separate study.

The systemic safety of ceftiofur concentrations resulting from product administration at the base of the ear was established via a pharmacokinetic comparison of the two routes of administration (base of the ear versus middle third of the ear). Based upon the results of this relative bioavailability study, it was determined that the two routes of administration are therapeutically equivalent.

To support systemic target animal safety for the 2-dose metritis regimen, five projected daily doses of NAXCEL Sterile Powder (ceftiofur sodium) at 2.2 mg/kg BW were compared pharmacokinetically with EXCEDE administered 2 times at a 72 hour interval at 6.6 mg/kg BW. The peak concentration (C_{max}) and the extent of exposure (AUC) after two doses of EXCEDE were statistically no higher than the exposure following five daily doses of NAXCEL Sterile Powder in beef cattle.

Investigation of Intra-Arterial and Intravenous Injection

In approximately 6000 animals enrolled in the BRD clinical studies, nine animals died following injection of EXCEDE Sterile Suspension. All deaths were within 30 minutes of the time of injection. The exact cause was confirmed in three animals. These deaths resulted from inadvertent intra-arterial injection of this oil-based suspension into one of the two major auricular (ear) arteries. Intra-arterial injection at this location resulted in direct administration of EXCEDE Sterile Suspension formulation into the arterial blood supply of the brain resulting in embolism and death.

Since intra-arterial injection was confirmed in three animals that died following injection of EXCEDE Sterile Suspension, the consequences of purposeful intra-arterial injection of EXCEDE Sterile Suspension were investigated in feeder cattle. Two heifers (body weight approximately 225 kg) were given a single 3.0 mg CE/lb (6.6 mg CE/kg) BW bolus dose of EXCEDE Sterile Suspension in the middle auricular artery. Both heifers collapsed immediately and died within approximately eight minutes of injection. Intra-arterial injection of EXCEDE Sterile Suspension in the ear will result in death and must be avoided.

Since subcutaneous injection in the ear may potentially result in inadvertent intravenous administration of an injectable product, the consequences of purposeful intravenous injection of EXCEDE Sterile Suspension were investigated in feeder cattle. Three heifers and three steers (body weight range 197-223 kg) were given a single 3.0 mg CE/lb (6.6 mg CE/kg) BW bolus dose of EXCEDE Sterile Suspension in the jugular vein and were monitored for adverse effects following injection. One steer and one heifer had transient (2 to 5 minutes) increases in heart rate without any other untoward signs in these or the other cattle. Intravenous injection of EXCEDE Sterile Suspension is an unacceptable route of administration.

Safety Studies in Beef Cattle

Middle of the ear injection:

A study was designed and conducted to specifically address tissue tolerance in cattle when EXCEDE Sterile Suspension was administered as a single subcutaneous injection into the posterior aspect of the ear of cattle at the recommended dose of 3.0 mg CE/lb (6.6 mg CE/kg) BW. Results from this study indicate that the subcutaneous injection of EXCEDE Sterile Suspension into the middle third of the posterior aspect of the ear of cattle is well tolerated and characterized by a biphasic thickening of the ear. The initial increase in thickness is attributed to the space required for the volume of injected material. Additional increases in thickness were observed through Day 14 after injection. After Day 14, post injection ear thickness decreased in all animals. One animal carried an injected ear in a drooping position for 7 days post injection. At necropsy, subcutaneous areas of discoloration and some foci of hemorrhage were observed in ears of injected cattle. The discoloration was markedly reduced in size by the end of the study. Ears are inedible tissues in the US (9 CFR 301.2). No signs of irritation were observed on the edible portions of the carcass around the base of the ear.

The local tolerance of the ear of cattle to a single subcutaneous injection of EXCEDE Sterile Suspension was also evaluated in a large multi-location effectiveness study. None of the 1927 animals treated with EXCEDE Sterile Suspension were removed from this trial due to ear irritation although swelling was noted at some injection sites. Leak back and/or bleeding from the injection site was observed in a small fraction of the treated animals immediately after administration. It was concluded that administration of EXCEDE Sterile Suspension in the posterior aspect of the ear was well tolerated and was acceptable under feedlot conditions.

A study evaluated the 56-day feedlot performance of beef steers administered EXCEDE Sterile Suspension alone, EXCEDE Sterile Suspension with a growth promoting implant, growth promoting implant alone, or neither product, in a total of 207 Angus and Angus cross-bred steers. The administration of EXCEDE Sterile Suspension in the posterior aspect of the ear with or without growth promoting implants was well tolerated by cattle and did not adversely affect feedlot cattle performance. Based upon the results of this study, the location of implants administered after EXCEDE Sterile Suspension may need to be adjusted slightly within the boundaries of the middle third of the ear in some animals.

Base of the ear injection:

The local tolerance of the ear to a single subcutaneous injection at the base of the ear of EXCEDE Sterile Suspension was evaluated in a multi-location field study in 2926 beef cattle. Normal restraint was adequate for administration of EXCEDE Sterile Suspension for 99.8% of cattle. No post injection problems (excessive bleeding or leak back) were observed in 99.8% of cattle. On Days 28 and 56 post-injection, 97.8% and 98.9% of the cattle had "normal" (no observed swelling) ears.

In a residue study, 72 beef cattle were injected in the base of the ear with EXCEDE Sterile Suspension at a dose rate of 3.0 mg CE/lb (6.6 mg CE/kg) BW. Injection sites were observed daily from treatment to necropsy (4, 7, 10, or 13 days post-injection) for swelling and drooping, and evaluated grossly at necropsy, using skinning and trimming procedures similar to slaughterhouse practices. All animals had injection site swelling during the study; swelling resolved prior to euthanasia in 23 of 72 animals. None of the animals showed ear drooping. At necropsy, signs of inflammation (hemorrhage, congestion, and firmness of tissue) and presence of drug material were seen in the area around the injection site and on the carcass. At 13 days post-injection, gross lesions were found in the inedible portions of the base of the ear in all 18 animals, and in the exposed carcass tissue in 11 of 18 animals.

The ventral base of the ear injection technique was evaluated in a conditions of use study in 200 beef cattle. Each animal received a single injection of EXCEDE Sterile Suspension at a dose of 6.6 mg CE/kg BW at the base of the ear using the ventral injection technique. Normal restraint was adequate for 95.5% of animals in the study. Injection site scores were normal for 65.3% and 92.5% of cattle on Days 14 and 28, respectively. One animal had an unusually large swelling on Day 7 which reduced to a size comparable to other study animals by Day 14.

Safety Studies in Lactating Dairy Cattle

The local tolerance of the ear to a single subcutaneous injection at the base of the ear of EXCEDE Sterile Suspension was evaluated in a multi-location field study in 114 adult dairy cattle. Successful injection in the base of the ear was achieved in 97.4% of cattle using normal facilities and restraint equipment. No leak back or excessive bleeding was observed following injection for 99.1% of cattle, with injection volumes ranging from 15 to 30 mL. On Days 28 and 56 following injection of EXCEDE Sterile Suspension in the base of the ear, 95.6% and 100% of ears, respectively, were observed as normal with no injection site swelling.

In a residue study, six dairy cows were injected in the base of the ear at a dose rate of 3.0 mg CE/lb (6.6 mg CE/kg) BW of EXCEDE Sterile Suspension. No animals exhibited drooping ears at any time after treatment but all animals had signs of swelling at the injection site at all observation times after treatment. Cows were slaughtered 10 days after injection. At necropsy, all six cows showed evidence of injection site inflammation (discoloration of fat tissue/fascia) and four of six cows had discoloration of tissue dorsal and posterior to the ear canal on the carcass. In addition to discoloration, tan nodules and a milky white fluid exudate were also present at the sectioned surface.

Injection site safety for base of the ear administration was evaluated in the metritis effectiveness study described above. Normal restraint was adequate for ≥ 97.8% of injections administered. Injection site scores were normal in 50.3%, 73.2%, and 96.4% at 2 or 3, 11, and 54±3 days after the second injection, respectively.

The ventral and rostral base of the ear injection techniques were compared with the toward the opposite eye technique in a conditions of use study in 197 lactating dairy cattle. Normal restraint was adequate for 89.8% (ventral), 98% (rostral), and 100% (opposite eye) of animals in the study. Injection site scores were normal for 32% (rostral), 46.9% (ventral), and 47.9% (opposite eye) of cattle on Day 14, and 73% (rostral), 87.8% (ventral), and 64.6% (opposite eye) of cattle on Day 28, respectively.

TISSUE AND MILK RESIDUE DEPLETION

A radiolabeled residue metabolism study established tolerances for ceftiofur residues in cattle kidney, liver and muscle. A separate study established the tolerance for ceftiofur residues in milk. The tolerances for ceftiofur residues are 0.4 ppm in kidney, 2.0 ppm in liver, 1.0 ppm in muscle and 0.1 ppm in milk.

A pivotal tissue residue depletion study was conducted in dairy cattle. In this study, cows received a single injection of 3.0 mg CE/lb (6.6 mg CE/kg) BW. Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in tissues such as the kidney, liver and muscle by 13 days after dosing. These data collectively support a 13-day pre-slaughter withdrawal period.

A pivotal milk residue decline study was conducted in lactating dairy cattle. In this study, cows received a single injection of 3.0 mg CE/lb (6.6 mg CE/kg) BW. Ceftiofur residues in milk were less than the tolerances at all time points after treatment. These data collectively support that no milk discard period is required for this product.

Two-Dose Residue Decline Studies

A pivotal tissue residue decline study was conducted in dairy cattle. In this study, cows received two injections of 3.0 mg CE/lb (6.6 mg CE/kg) BW with a 72 hour interval between injections. Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in the kidney by 13 days after the second dose. These data collectively continue to support a 13-day pre-slaughter withdrawal period after the last dose.

A pivotal milk residue decline study was conducted in lactating dairy cattle. In this study, cows received two injections of 3.0 mg CE/lb (6.6 mg CE/kg) BW with a 72 hour interval between injections. Milk residue decline data from this study supports that no milk discard period is required for this product.

STORAGE CONDITIONS

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

HOW SUPPLIED

EXCEDE Sterile Suspension is available in the following package sizes:
100 mL vial
250 mL vial

NADA #141-209, Approved by FDA

www.EXCEDE.com or call 1-866-387-2287

Revised: December 2011 EXD12042

Distributed by
Pharmacia & Upjohn Company
Division of Pfizer Inc, NY, NY 10017

Naxcel®

brand of ceftiofur sodium sterile powder

For intramuscular and subcutaneous injection in cattle only. For intramuscular injection in swine, sheep, goats, and horses. For subcutaneous injection only in dogs, day-old chickens and day-old turkey poults. This product may be used in lactating dairy cattle, sheep, and goats.

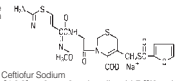
CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

NAXCEL Sterile Powder contains the sodium salt 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 the reconstituted drug contains ceftiofur sodium equivalent to 50 mg ceftiofur. The pH was adjusted with sodium hydroxide and monobasic potassium phosphate.

Chemical Structure of Ceftiofur Sodium



Chemical Name of Ceftiofur Sodium

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[[2-amino-4-thiazolyl)(methoxyimino)-acetyl]amino]-3-[[(2-furanyl-carbonyl)thio]methyl]-8-oxo-, monosodium salt, [6R-[6α,7β (Z)]]-

RECONSTITUTION OF THE STERILE POWDER

NAXCEL Sterile Powder should be reconstituted as follows:

1 gram vial—Reconstitute with 20 mL Sterile Water for Injection. Each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur.

4 gram vial—Reconstitute with 80 mL Sterile Water for Injection. Each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur.

Shake thoroughly prior to use.

INDICATIONS

Cattle

NAXCEL Sterile Powder is indicated for treatment of bovine respiratory disease (shipping fever, pneumonia) associated with *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni*. 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*.

Sheep

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

Goats

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

Horses

NAXCEL Sterile Powder is indicated for treatment of respiratory infections in horses associated with *Streptococcus zooepidemicus*.

Dogs

NAXCEL Sterile Powder is indicated for the treatment of canine urinary tract infections associated with *Escherichia coli* and *Proteus mirabilis*.

Day-Old Chicks

NAXCEL Sterile Powder is indicated for the control of early mortality, associated with *E. coli* organisms susceptible to ceftiofur, in day-old chicks.

Day-Old Turkey Poults

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

DOSAGE AND ADMINISTRATION

Cattle

Administer to cattle by intramuscular or subcutaneous injection at the dosage of 0.5 to 1.0 mg ceftiofur per pound (1.1 to 2.2 mg/kg) of body weight (1-2 mL reconstituted sterile solution per 100 lbs body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days. Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the initial three treatments. Selection of dosage (0.5 to 1.0 mg/lb) should be based on the practitioner's judgement of severity of disease (i.e., for respiratory disease, extent of elevated body temperature, depressed physical appearance, increased respiratory rate, coughing and/or loss of appetite; and for foot rot, extent of swelling, lesion and severity of lameness).

Swine

Administer to swine by intramuscular injection at the dosage of 1.36 to 2.27 mg ceftiofur per pound (3.0 to 5.0 mg/kg) of body weight (1 mL of reconstituted sterile solution per 22 to 37 lbs body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days.

Sheep

Administer to sheep by intramuscular injection at the dosage of 0.5 to 1.0 mg ceftiofur per pound (1.1 to 2.2 mg/kg) of body weight (1-2 mL reconstituted sterile solution per 100 lbs of body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days. Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the initial three treatments. Selection of dosage (0.5 to 1.0 mg/lb) should be based on the practitioner's judgement of severity of disease (i.e., extent of elevated body temperature, depressed physical appearance, increased respiratory rate, coughing and/or loss of appetite).

Goats

Administer to goats by intramuscular injection at the dosage of 0.5 to 1.0 mg ceftiofur per pound (1.1 to 2.2 mg/kg) of body weight (1-2 mL reconstituted sterile solution per 100 lbs body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days. Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the initial three treatments. Selection of dosage (0.5 to 1.0 mg/lb) should be based on the practitioner's judgement of severity of disease (i.e., extent of elevated body temperature, depressed physical appearance, increased respiratory rate; coughing and/or loss of appetite). Pharmacokinetic data indicate that elimination of the drug is more rapid in lactating does. For lactating does, the high end of the dose range is recommended.

Horses

Administer to horses by intramuscular injection at the dosage of 1.0 to 2.0 mg ceftiofur per pound (2.2 to 4.4 mg/kg) of body weight (2-4 mL reconstituted sterile solution per 100 lbs body weight). A maximum of 10 mL may be administered per injection site. Treatment should be repeated at 24-hour intervals, continued for 48 hours after clinical signs have disappeared and should not exceed 10 days.

Dogs

Administer to dogs by subcutaneous injection at the dosage of 1.0 mg ceftiofur per pound (2.2 mg/kg) of body weight (0.1 mL reconstituted sterile solution per 5 lbs body weight). Treatment should be repeated at 24-hour intervals for 5-14 days.

Reconstituted NAXCEL Sterile Powder is to be administered to dogs by subcutaneous injection. No vial closure should be entered more than 20 times. Therefore, only the 1 gram vial is approved for use in dogs.

Day-Old Chicks

Administer by subcutaneous injection in the neck region of day-old chicks at the dosage of 0.08 to 0.20 mg ceftiofur/chick. One mL of the 50 mg/mL reconstituted solution will treat approximately 250 to 625 day-old chicks.

Reconstituted NAXCEL Sterile Powder is to be administered by subcutaneous injection only. A sterile 26 gauge needle and syringe or properly cleaned automatic injection machine should be used.

Day-Old Turkey Poults

Administer by subcutaneous injection in the neck region of day-old turkey poults at the dosage of 0.17 to 0.5 mg ceftiofur/poult. One mL of the 50 mg/mL reconstituted solution will treat approximately 100 to 294 day-old turkey poults.

Reconstituted NAXCEL Sterile Powder is to be administered by subcutaneous injection only.

CONTRAINDICATIONS

As with all drugs, the use of NAXCEL Sterile Powder is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS

NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.

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.

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 event please call 1-800-366-5288.

RESIDUE WARNINGS:

Cattle: When used according to label indications, dosage and routes of administration, treated cattle must not be slaughtered for 4 days following the last treatment. When used according to label indications, dosage and routes of administration, a milk discard time is not required. **Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or in milk.**

Swine: When used according to label indications, dosage and route of administration, treated pigs must not be slaughtered for 4 days following the last treatment. **Use of dosages in excess of those indicated or by unapproved routes of administration may result in illegal residues in edible tissues.**

Sheep: Neither a pre-slaughter drug withdrawal interval nor a milk discard time is required when this product is used according to label indications, dosage, and route of administration. **Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or in milk.**

Goats: Neither a pre-slaughter drug withdrawal interval nor a milk discard time is required when this product is used according to label indications, dosage, and route of administration. **Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or in milk.**

Horses: Do not use in horses intended for human consumption.

PRECAUTIONS

The effects of ceftiofur on the reproductive performance, pregnancy and lactation of cattle, swine, sheep, and goats have not been determined.

Cattle

Following subcutaneous administration of ceftiofur sodium in the neck, small areas of discoloration at the site may persist beyond five days, potentially resulting in trim loss of edible tissues at slaughter.

As with any parenteral injection, localized post-injection bacterial infections may result in abscess formation. Attention to hygienic procedures can minimize their occurrence.

Swine

The safety of ceftiofur has not been determined for swine intended for breeding.

Horses

The safety of ceftiofur has not been determined for horses intended for breeding. The administration of antimicrobials to horses under conditions of stress may be associated with acute diarrhea that could be fatal. If acute diarrhea is observed, discontinue use of this antimicrobial and initiate appropriate therapy.

Dogs

The safety of ceftiofur has not been determined for dogs intended for breeding, or pregnant dogs.

ADVERSE REACTIONS

The use of ceftiofur may result in some signs of immediate and transient local pain to the animal.

CLINICAL MICROBIOLOGY

Summaries of MIC data are presented in Tables 1 and 2. Testing followed Clinical and Laboratory Standards Institute (CLSI) Guidelines.

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) BW (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 CLSI.

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. Alternately 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.

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 CLSI.

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.

Standardized procedures[1] require the use of laboratory control organisms for both standardized diffusion techniques and standardized 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 strain. Ceftiofur sodium disks or powder reference standard is appropriate for both ceftiofur salts.

ANIMAL SAFETY

Cattle

Results from a five-day tolerance study in normal feeder calves indicated that formulated ceftiofur was well tolerated at 25 times (25 mg/lb/day) the highest recommended dose of 1.0 mg/lb/day for five consecutive days. Ceftiofur administered intramuscularly had no adverse systemic effects.

In a 15-day safety/toxicity study, five steer and five heifer calves per group were intramuscularly administered formulated ceftiofur at 0 (vehicle control), 1, 3, 5 and 10 times the highest recommended dose of 1.0 mg/lb/day to determine the safety factor. There were no adverse systemic effects indicating that the formulated ceftiofur has a wide margin of safety when injected intramuscularly into the feeder calves at 10 times (10 mg/lb/day) the recommended dose for three times (15 days) the recommended three to five days of therapy. The formulation was shown to be a slight muscle irritant based on results of histopathological evaluation of the injection sites at 1 and 3 times the highest recommended dose of 1.0 mg/lb/day. The histopathological evaluations were conducted at posttreatment days 1, 3, 7 and 14.

The injection of NAXCEL Sterile Powder at the recommended dose administered SC in the neck of cattle was well tolerated. However, a several square centimeter area of yellowed discoloration resulting from a single SC injection persisted in many of the cattle beyond 4.5 days post-injection. Also, one of the animals developed an abscess at the injection site.

Swine

Results from a five-day tolerance study in normal feeder pigs indicated that formulated ceftiofur was well tolerated when administered at 57 mg/lb (more than 25 times the highest recommended daily dosage of 2.27 mg/lb of body weight) for five consecutive days. Ceftiofur administered intramuscularly to pigs produced no overt adverse signs of toxicity.

Table 1. Ceftiofur MIC Values of Bacterial Isolates from Clinical Field Studies in the USA

Organism	Number Tested	Date Tested	MIC_{50}* (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
Histophilus somni	109	1988–1992	0.06	≤0.03–0.13
Histophilus somni	59	1993	≤0.0019	no range
Fusobacterium necrophorum	17	1994	≤0.06	no range
SWINE				
Actinobacillus pleurpn.	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.

Table 2. Ceftiofur MIC Values of Bacterial Isolates from Diagnostic Laboratories in the USA and Canada*

Organism	Number Tested	Date Tested	MIC_{50}** (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
Histophilus somni	48	1997–1998	≤0.03	≤0.03–0.25
Histophilus somni	87	1998–1999	≤0.03	≤0.03–0.125
Histophilus somni	77	1999–2000	≤0.03	≤0.03–0.12
Histophilus somni	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 pleurpn.	97	1997–1998	≤0.03	no range
Actinobacillus pleurpn.	111	1998–1999	≤0.03	≤0.03–0.25
Actinobacillus pleurpn.	126	1999–2000	≤0.03	≤0.03–0.06
Actinobacillus pleurpn.	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
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	22	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–>32.0
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	0.12–0.5
Escherichia coli	20	2000-2001	2.0	0.12–16.0
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–>4.0
Escherichia coli	67	1999-2000	0.50	0.12–16.0
Escherichia coli	90	2000-2001	1.0	≤0.03–8.0

* 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.

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 No.)	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***
Histophilus somni (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).

To determine the safety factor and to measure the muscle irritancy potential in swine, a safety/toxicity study was conducted. Five barrows and five gilts per group were intramuscularly administered formulated ceftiofur at 0, 2.27, 6.81 and 11.36 mg/lb of body weight for 15 days which is 0, 1, 3 and 5 times the highest recommended dose of 2.27 mg/lb of body weight/day and 5 times the recommended treatment length of 3 days. There were no adverse systemic effects indicating that formulated ceftiofur has a wide margin of safety when injected intramuscularly into feeder pigs at the highest recommended dose of 2.27 mg/lb/day for 3 days or at levels up to 5 times the highest recommended dose for 5 times the recommended length of treatment.

The formulation was shown to be a slight muscle irritant based on results of histopathological evaluation of the injection sites at posttreatment days 1, 2, 3 and 4. By day 10 post injection the muscle reaction was subsiding and at day 15 post injection there was little evidence of muscle damage in any of the pigs in any of the treatment groups.

Sheep

In a 15-day safety/toxicity study in sheep, three wether and three ewe lambs per group were given formulated ceftiofur sodium by the intramuscular route 0 (sterile water vehicle), 1, 3 or 5 times the recommended dose of 1.0 mg/lb/day for 3 times the recommended maximum duration of 5 days of treatment. There were no adverse systemic effects indicating that formulated ceftiofur is well tolerated and has a wide margin of safety in sheep. Based on examination of injection sites from study days 9, 11, 13 and 15, a low incidence of visual changes and histopathologic findings of mild, reversible inflammation that all goes including the controls indicated that the formulation is a slight muscle irritant.

Goats

In a 15-day safety/toxicity study 5 lactating does, 5 dry does, and 5 wethers were given formulated ceftiofur by the intramuscular route with 11 mg/kg/day for 15 days. This constitutes 5 times the recommended dose for 3 times the recommended maximum duration of 5 days of treatment. There were no adverse systemic effects indicating that formulated ceftiofur is well tolerated and has a wide margin of safety in goats.

Horses

In a safety study, horses received a daily intramuscular injection of either 0 mg/lb/day (saline control), 1.0 mg/lb/day (50 mg/mL), 3.0 mg/lb/day (100 mg/mL), or 5.0 mg/lb/day (200 mg/mL) of an aqueous solution of ceftiofur sodium for 30 or 31 days. Ceftiofur sodium was well tolerated when administered intramuscularly to male and female horses at doses up to 5.0 mg/lb/day for 30 or 31 days. No clinical evidence of irritation was noted at any dose. The drug-related changes detected in this study were limited to a transient decrease in food consumption in horses receiving 3.0 or 5.0 mg/lb/day ceftiofur, and general mild skeletal muscle irritation at the injection sites which resolved by regeneration of muscle fibers.

In a tolerance study, horses received a single daily intravenous infusion of either 0 (saline), 10.0 or 25.0 mg/lb/day of an aqueous solution (50 mg/mL) of ceftiofur for 10 days. The results indicated that ceftiofur administered intravenously at a dose of 10.0 or 25.0 mg/lb/day apparently can change the bacterial flora of the large intestine thereby leading to inflammation of the large intestine with subsequent diarrhea and other clinical signs (loose feces, eating bedding straw, dehydration, rolling or colic and a dull, inactive demeanor). Decreased food consumption, a loss of body weight, hematologic changes related to acute inflammation and stress, and serum chemistry changes related to decreased food consumption and diarrhea were also associated with treatment at these doses. The adverse effects were most severe a few days after dosing was initiated and tended to become less severe toward the end of the 10-day dosing period.

Dogs

Ceftiofur sodium was well tolerated at the therapeutic dose and is safe for the treatment of urinary tract infections in dogs. In the acute safety study, ceftiofur was well tolerated by dogs at the recommended level (1.0 mg/lb) for 5-14 days. When administered subcutaneously for 42 consecutive days, one of four females developed thrombocytopenia (15 days) and anemia (36 days). Thrombocytopenia and anemia also occurred at the 3X and 5X dose levels. In the reversibility phase of the study (5X dose), the thrombocytopenia reversed within 8 days, and of the two anemic animals the male recovered within 6 weeks and the female was sacrificed due to the severity of the anemia.

In the 15-day tolerance study in dogs, high subcutaneous doses (25 and 125 times the recommended therapeutic dose) produced a progressive and dose-related thrombocytopenia, with some dogs also exhibiting anemia and bone marrow changes. The hematopoietic changes noted in dogs treated with ceftiofur were similar to those associated with long-term cephalosporin administration in dogs and also man. The hematopoietic effects are not expected to occur as a result of recommended therapy.

Day-Old Chicks

In an acute toxicity study of ceftiofur in day-old chicks, a total of 60 male and 60 female chicks were each given single subcutaneous injections of 10, 100 or 1,000 mg/kg of body weight. Treatment on day 1 was followed by 6 days of observation; body weight was determined on days 1, 4 and 7; and selected hematology parameters were evaluated on day 4. No meaningful differences were noted among the treated and control groups of chicks for the parameters evaluated. Histopathologic evaluation of all deaths and chicks surviving to termination did not reveal a target organ or tissue of potential toxicity of ceftiofur when administered at up to 20 times (100 mg/kg) the intended highest use dosage.

Day-Old Turkey Poults

In an acute toxicity study of ceftiofur in day-old turkey poults, a total of 30 male and 30 female poults were each administered single subcutaneous injections of 100, 400 or 800 mg/kg body weight. Injection on day 1 was followed by 6 days of observation; body weight on days 1, 4, and 7; and selected hematology parameters on day 4. No meaningful differences were noted between the treated groups at 100 or 400 mg ceftiofur/kg and a negative control group for the parameters evaluated. Histopathologic evaluation of all deaths and pouts surviving to termination did not reveal a target organ or tissue of potential toxicity of ceftiofur when administered at up to 50 times (400 mg/kg) the highest use dosage. A dose of 800 mg/kg (100 times the intended highest use dosage) was toxic, resulting in clinical signs and deaths accompanied by gross and microscopic morphologic tissue alterations.

TISSUE RESIDUE DEPLETION

Cattle

A radiolabeled residue metabolism study established tolerances for ceftiofur residues in cattle kidney, liver and muscle. These tolerances of ceftiofur residues are 0.4 ppm in kidney, 2.0 ppm in liver, 1.0 ppm in muscle, and 0.1 ppm in milk.

A pivotal tissue residue decline study was conducted in cattle. In this study, cattle received an intramuscular injection of 1.0 mg of ceftiofur per lb body weight (2.2 mg of ceftiofur per kg body weight) for five consecutive days. Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in tissues such as kidney, liver and muscle by 4 days after dosing. These data collectively support a 4-day pre-slaughter withdrawal period in cattle when used according to label directions.

Swine

Radiolabeled residue metabolism studies established tolerances for ceftiofur residues in swine kidney, liver, and muscle. These tolerances of ceftiofur residues are 0.25 ppm in kidney, 3.0 ppm in liver and 2.0 ppm in muscle.

A pivotal tissue residue decline study was conducted in swine. In this study, pigs received 2.27 mg of ceftiofur per lb body weight (5 mg of ceftiofur per kg body weight) per day for three consecutive days. Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in tissues such as kidney, liver and muscle by 4 days after dosing. These data collectively support a 4-day pre-slaughter withdrawal period in swine when used according to label directions.

STORAGE CONDITIONS

Store **unreconstituted** product at controlled room temperature 20° to 25° C (68° to 77° F) [see USP].

Store **reconstituted** product either in a refrigerator 2° to 8° C (36° to 46° F) for up to 7 days or at controlled room temperature 20° to 25° C (68° to 77° F) [see USP] for up to 12 hours.

Protect from light. Color of the cake may vary from off-white to a tan color. Color does not affect potency.

ONE-TIME SALVAGE PROCEDURE FOR RECONSTITUTED PRODUCT

At the end of the 7-day refrigeration or 12-hour room temperature storage period following reconstitution, any remaining reconstituted product may be frozen for up to 8 weeks without loss in potency or other chemical properties. This is a one-time only salvage procedure for the remaining product. To use this salvaged product at any time during the 8-week storage period, hold the vial under warm running water, gently swirling the container to accelerate thawing, or allow the frozen material to thaw at room temperature. Rapid freezing or thawing may result in vial breakage. Any product not used immediately upon thawing should be discarded.

HOW SUPPLIED

NAXCEL Sterile Powder is available in the following package sizes:

1 gram vial
4 gram vial

1 Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals; Approved Standard – Second Edition. NCCLS document M31-A2. CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, 2002.

NADA # 140-338, Approved by FDA

Pfizer Animal Health
Distributed by
Pharmacia & Upjohn Company
Division of Pfizer Inc, NY, NY 10017

NAX12001
Revised February 2006
814 055 427
3362-03-000

EXCENEL® RTU EZ

(ceftiofur hydrochloride)

Sterile Suspension

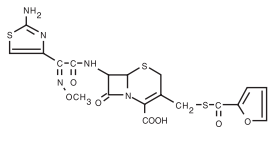
For intramuscular injection in swine. For intramuscular and subcutaneous injection in cattle. This product may be used in lactating dairy cattle. Not for use in calves to be processed for veal.

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Federal law prohibits extra-label use of this drug in cattle and swine for disease prevention purposes; at unapproved doses, frequencies, durations, or routes of administration; and in unapproved major food producing species/production classes.

DESCRIPTION

EXCENEL RTU EZ Sterile Suspension is a ready to use formulation that contains the hydrochloride salt of ceftiofur, which is a broad spectrum cephalosporin antibiotic. Each mL of this ready-to-use sterile suspension contains ceftiofur hydrochloride equivalent to 50 mg ceftiofur, 2.50 mg polyoxyethylene sorbitan monooleate (polysorbate 80), 6.5 mg water for injection in a caprylic/capric triglyceride (Miglyol® 812) suspension.

Figure 1. Structure:



• HCl

Chemical Name of Ceftiofur Hydrochloride: 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)-acetyl]amino]-3-[[(2-furanylcarbonyl)thio]methyl]-8-oxo-,hydrochloride salt [6R-[6α,7β(Z)]]-

INDICATIONS

Swine: EXCENEL RTU EZ Sterile Suspension is indicated for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Salmonella* Choleraesuis and *Streptococcus suis*.

Cattle: EXCENEL RTU EZ Sterile Suspension is indicated for treatment of the following bacterial diseases:

— Bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni*.

— Acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.

— Acute metritis (0 to 14 days post-partum) associated with bacterial organisms susceptible to ceftiofur.

DOSAGE AND ADMINISTRATION

Shake well before using.

Swine: Administer intramuscularly at a dosage of 1.36 to 2.27 mg ceftiofur equivalents (CE)/lb (3 to 5 mg CE/kg) body weight (BW) (1 mL of sterile suspension per 22 to 37 lb BW). Treatment should be repeated at 24 hour intervals for a total of three consecutive days. Do not inject more than 5 mL per injection site.

Cattle:

— For bovine respiratory disease and acute bovine interdigital necrobacillosis: administer by intramuscular or subcutaneous administration at the dosage of 0.5 to 1 mg CE/lb (1.1 to 2.2 mg CE/kg) BW (1 to 2 mL sterile suspension per 100 lb BW). Administer daily at 24 hour intervals for a total of three consecutive days. Additional treatments may be administered on Days 4 and 5 for animals which do not show a satisfactory response (not recovered) after the initial three treatments. In addition, for BRD only, administer intramuscularly or subcutaneously 1 mg CE/lb (2.2 mg CE/kg) BW every other day on Days 1 and 3 (48 hour interval). Do not inject more than 15 mL per injection site.

Selection of dosage level (0.5 to 1 mg CE/lb) and regimen/duration (daily or every other day for BRD only) should be based on an assessment of the severity of disease, pathogen susceptibility and clinical response.

— For acute post-partum metritis: administer by intramuscular or subcutaneous administration at the dosage of 1 mg CE/lb (2.2 mg CE/kg) BW (2 mL sterile suspension per 100 lb BW). Administer at 24 hour intervals for five consecutive days. Do not inject more than 15 mL per injection site.

CONTRAINDICATIONS

As with all drugs, the use of EXCENEL RTU EZ Sterile Suspension is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS

NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.

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.

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) or to report any adverse event please call 1-888-963-8471.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/AnimalVeterinary/SafetyHealth.

RESIDUE WARNINGS:

Swine: When used according to label indications, dosage and route of administration, treated swine must not be slaughtered for 4 days following the last treatment. Use of dosages in excess of those indicated or by unapproved routes of administration may result in illegal residues in edible tissues.

Cattle: When used according to label indications, dosage and route of administration, treated cattle must not be slaughtered for 4 days following the last treatment. When used according to label indications, dosage and route of administration, a milk discard time is not required. Uses of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or milk. A withdrawal period has not been established in pre-ruminating calves. Do not use in calves to be processed for veal.

PRECAUTIONS

The effects of ceftiofur on cattle and swine reproductive performance, pregnancy and lactation have not been determined.

Intramuscular and subcutaneous injection in cattle and intramuscular injection in swine can cause a transient local tissue reaction that may result in trim loss of edible tissue at slaughter.

CLINICAL PHARMACOLOGY

Swine: Ceftiofur administered as either ceftiofur sodium or ceftiofur hydrochloride is metabolized rapidly to desfuroylceftiofur, the primary metabolite. Administration of ceftiofur to swine as either the sodium or hydrochloride salt provides effective concentrations of ceftiofur and desfuroylceftiofur metabolites in plasma above the lowest minimum inhibitory concentration to encompass 90% of the most susceptible isolates (MIC90) for the labeled pathogens: *Actinobacillus pleuropneumoniae*, *Pasteurella multocida, Streptococcus suis* and *Salmonella* Choleraesuis for the 24 hour period between the dosing intervals. The MIC_{90} for *Salmonella* Choleraesuis (1.0 µg/mL) is higher than the other three pathogens and plasma concentrations exceed this value for the entire dosing interval only after the 2.27 mg/lb (5.0 mg/kg) BW dose.

Comparative Bioavailability Summary

The current EXCENEL RTU EZ Sterile Suspension formulation replaces a previously approved formulation. The previously approved EXCENEL RTU EZ product was a reformulation of another ceftiofur hydrochloride injectable product, EXCENEL RTU Sterile Suspension (NADA 140-890). Comparable plasma concentrations of ceftiofur administered as EXCENEL RTU Sterile Suspension or the reformulated EXCENEL RTU EZ Sterile Suspension were demonstrated in a comparative two-treatment, two-period crossover relative bioavailability study in swine. Products were administered via intramuscular (IM) injection into the neck, using alternating sides during periods 1 and 2. A summary of average plasma pharmacokinetic (PK) parameters in swine after a single IM administration of EXCENEL RTU Sterile Suspension and EXCENEL RTU EZ Sterile Suspension at a dose of 2.27 mg CE/lb (5.0 mg CE/kg) BW is provided in Table 1.

Table 1: Comparative treatment values (arithmetic mean ± SD) for the plasma PK estimates of total ceftiofur (parent compound plus desfuroylceftiofur metabolites) in swine following an IM administration of 2.27 mg CE/lb (5.0 mg CE/kg) BW, as either EXCENEL RTU (reference article) or as EXCENEL RTU EZ Sterile Suspension (test article).

PK Parameter	EXCENEL RTU	EXCENEL RTU EZ
C_{max} (µg/mL)	18.2 ± 4.09	19.7 ± 3.39
$AUC_{0\text{-}LOQ}$ (µg*h/mL)	257 ± 57.1	263 ± 54.8
t_{max} (h)	1.5 ± 0.49	1.5 ± 0.73
$t_{1/2}$ (h)	20.0 ± 1.56	20.0 ± 1.82
$t_{>0.2}$ (h)	83.1 ± 10.3	82.5 ± 10.5

C_{max} - maximum plasma concentration

$AUC_{0\text{-}LOQ}$ - the area under the plasma concentration vs. time curve from time of injection to the limit of quantification of the assay

t_{max} - the time after initial injection to when C_{max} occurs

$t_{1/2}$ - the plasma half life of the drug

$t_{>0.2}$ - the time plasma concentrations remain above 0.2 µg/mL.

The standard bioequivalence (BE) criteria, based upon the exponentiated 90% confidence bounds about the ratio of treatment means, were met for the pivotal bioequivalence parameters, $AUC_{0\text{-}LOQ}$ and C_{max}, when each formulation was administered to swine IM at a dose rate of 2.27 mg CE/lb (5.0 mg CE/kg) BW (Table 2).

Table 2: Back-transformed least squares (LS) means and 90% confidence interval (CI) for the two pivotal pharmacokinetic parameters, C_{max} and $AUC_{0\text{-}LOQ}$ in swine following an IM administration of 2.27 mg CE/lb (5.0 mg CE/kg) BW, as either EXCENEL RTU (reference article) or as EXCENEL RTU EZ Sterile Suspension (test article).

PK Parameter	LS Mean Difference	90% CI	BE†
C_{max}	1.10	1.03 to 1.18	Yes
$AUC_{0\text{-}LOQ}$	1.03	0.99 to 1.06	Yes

† If the 90% CI of the LS mean difference is within the limits of 0.80 to 1.25, then the results support bioequivalence of treatment groups

In another comparative bioavailability PK study (previously reviewed under NADA 140-890), comparable plasma concentrations of ceftiofur, administered as EXCENEL RTU Sterile Suspension or as NAXCEL Sterile Powder, were demonstrated when each product was administered intramuscularly at the upper end of the label dose range [2.27 mg CE/lb (5.0 mg CE/kg) BW]. The bioequivalence criteria were met for the $AUC_{0\text{-}LOQ}$, C_{max}, and $t_{>0.2}$ when both products were administered by an intramuscular injection to swine at a dose rate of 5.0 mg CE/kg BW.

Cattle: Ceftiofur administered as either ceftiofur sodium or ceftiofur hydrochloride is metabolized rapidly to desfuroylceftiofur, the primary metabolite. Administration of ceftiofur to cattle as either the sodium or hydrochloride salt provides effective concentrations of ceftiofur and desfuroylceftiofur metabolites in plasma above the MIC_{90} for the label BRD pathogens *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni* for at least 48 hours. The relationship between plasma concentrations of ceftiofur and desfuroylceftiofur metabolites above the MIC_{90} in plasma and effectiveness has not been established for the treatment of bovine interdigital necrobacillosis (foot rot) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.

Comparative Bioavailability Summary

The current EXCENEL RTU EZ Sterile Suspension formulation replaces a previously approved formulation. The previously approved EXCENEL RTU EZ product was a reformulation of another ceftiofur hydrochloride injectable product, EXCENEL RTU Sterile Suspension (NADA 140-890). Comparable plasma concentrations of ceftiofur administered as EXCENEL RTU Sterile Suspension and the reformulated EXCENEL RTU EZ Sterile Suspension were demonstrated in two comparative two-treatment, two-period crossover relative bioavailability studies in cattle. Products were administered via intramuscular (IM) or subcutaneous (SC) injection, using alternating sides of the neck during periods 1 and 2. A summary of average plasma pharmacokinetic (PK) parameters in cattle after a single IM and SC administration of EXCENEL RTU Sterile Suspension and EXCENEL RTU EZ Sterile Suspension at a dose of 1.0 mg CE/lb (2.2 mg CE/kg) BW is provided in Table 3.

Table 3: Comparative treatment values (arithmetic mean ± SD) for the plasma PK estimates of total ceftiofur (parent compound plus desfuroylceftiofur metabolites) in cattle following an IM or SC administration of 1.0 mg CE/lb (2.2 mg CE/kg) BW, as either EXCENEL RTU (reference article) or as EXCENEL RTU EZ Sterile Suspension (test article).

PK Parameter	IM		SC	
	EXCENEL RTU	EXCENEL RTU EZ	EXCENEL RTU	EXCENEL RTU EZ
C_{max} (µg/mL)	8.58 ± 1.50	9.25 ± 1.73	8.40 ± 1.42	9.19 ± 1.65
$AUC_{0\text{-}LOQ}$ (µg*h/mL)	89.4 ± 13.8	88.5 ±17.0	86.7 ± 20.3	91.0 ± 20.2
t_{max} (h)	1.71 ± 0.706	1.73 ± 0.489	2.08 ± 0.670	2.25 ± 0.872
$t_{1/2}$ (h)	32.0 ± 8.48	29.3 ± 7.35	34.0 ± 8.52	32.9 ± 6.91
$t_{>0.2}$ (h):	42.2 ± 6.20	41.2 ± 6.11	40.5 ± 5.28	41.5 ± 7.32

C_{max} - maximum plasma concentration

$AUC_{0\text{-}LOQ}$ - the area under the plasma concentration vs. time curve from time of injection to the limit of quantification of the assay

t_{max} - the time after initial injection to when C_{max} occurs

$t_{1/2}$ - the plasma half life of the drug

$t_{>0.2}$ - the time plasma concentrations remain above 0.2 µg/mL

The standard bioequivalence (BE) criteria, based upon the exponentiated 90% confidence bounds about the ratio of treatment means, were met for the pivotal bioequivalence parameters, $AUC_{0\text{-}LOQ}$ and C_{max}, when each formulation was administered to cattle IM or SC at a dose rate of 1.0 mg CE/lb (2.2 mg CE/kg) BW (Table 4).

Table 4: Back-transformed least squares (LS) means and 90% confidence intervals (CI) for the two pivotal pharmacokinetic parameters, C_{max} and $AUC_{0\text{-}LOQ}$ in cattle following an IM and SC administration of 1.0 mg CE/lb (2.2 mg CE/kg) BW, as either EXCENEL RTU (reference article) or as EXCENEL RTU EZ Sterile Suspension (test article).

PK Parameter	IM		SC	
	LS Mean Difference	90% CI	LS Mean Difference	90% CI
C_{max}	1.08	1.00 to 1.16	1.09	1.02 to 1.18
$AUC_{0\text{-}LOQ}$	0.984	0.94 to 1.03	1.06	0.99 to 1.13

In another comparative bioavailability PK study (previously reviewed under NADA 140-890), comparable plasma concentrations of ceftiofur administered as EXCENEL RTU Sterile Suspension or as NAXCEL Sterile Powder were demonstrated when each product was administered intramuscularly or subcutaneously at the approved dose range of ceftiofur sodium [0.5 to 1.0 mg CE/lb (1.1 to 2.2 mg CE/kg) BW].

MICROBIOLOGY

EXCENEL RTU EZ Sterile Suspension is a ready-to-use formulation that contains the hydrochloride salt of ceftiofur. Ceftiofur is a broad-spectrum cephalosporin antibiotic active against Gram-positive and Gram-negative bacteria. Like other cephalosporins, ceftiofur is predominantly bactericidal *in vitro*, resulting in the inhibition of cell wall synthesis. *In vitro* activity of ceftiofur has been demonstrated against *Actinobacillus pleuropneumoniae, Pasteurella multocida,* and *Salmonella* Choleraesuis, three pathogens associated with swine respiratory disease. Similarly, *in vitro* activity of ceftiofur has been demonstrated against *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni,* the three major pathogens associated with bovine respiratory disease, and against *Fusobacterium necrophorum* and *Bacteroides melaninogenicus,* pathogenic anaerobic bacteria associated with bovine foot rot.

Utilizing data that included isolates from swine and cattle affected by respiratory disease, zone diameter and minimum inhibitory concentration (MIC) breakpoints were determined using standardized procedures from the Clinical and Laboratory Standards Institute (CLSI, formerly National Committee of Clinical Laboratory Standards) M31-A2. The CLSI-accepted interpretive criteria for ceftiofur against these Gram-negative pathogens are shown in Table 5.

Table 5: CLSI-accepted interpretive criteria for ceftiofur against swine and cattle respiratory pathogens.*

Pathogen	Disk potency	Zone diameter interpretive standards (mm)			MIC breakpoint (µg/mL)		
		S	I	R	S	I	R
Actinobacillus pleuropneumoniae *Pasteurella multocida* *Salmonella* Choleraesuis	30 µg	≥ 21	18 to 20	≤ 17	≤ 2.0	4.0	≥ 8.0
Mannheimia haemolytica *Pasteurella multocida* *Histophilus somni*							
S – Susceptible I – Intermediate R – Resistant							

* These interpretive criteria are only intended for use when CLSI M31-A2 performance standards are used to determine antimicrobial susceptibility.

EFFECTIVENESS

Swine: Plasma concentrations of ceftiofur administered as EXCENEL RTU Sterile Suspension or as EXCENEL RTU EZ Sterile Suspension following intramuscular administration in swine were compared and found to be bioequivalent for $AUC_{0\text{-}LOQ}$ and C_{max}. Therefore, EXCENEL RTU EZ Sterile Suspension has the same effectiveness profile as previously established for EXCENEL RTU Sterile Suspension. Because the effectiveness of cephalosporin antibiotics is dependent upon time above MIC, EXCENEL RTU EZ Sterile Suspension is considered effective for the treatment/control of swine respiratory disease.

Cattle: Plasma concentrations of ceftiofur administered as EXCENEL RTU Sterile Suspension or as EXCENEL RTU EZ Sterile Suspension following intramuscular or subcutaneous administration in cattle were compared and found to be bioequivalent for $AUC_{0\text{-}LOQ}$ and C_{max}. Therefore, EXCENEL RTU EZ Sterile Suspension has the same effectiveness profile as previously established for EXCENEL RTU Sterile Suspension. Because the effectiveness of cephalosporin antibiotics is dependent upon time above MIC, EXCENEL RTU EZ Sterile Suspension is considered effective for the labeled indications.

ANIMAL SAFETY

Swine: Evaluation of target animal safety in swine was based on a PK comparison between the reformulated EXCENEL RTU EZ Sterile Suspension and EXCENEL RTU Sterile Suspension. Ceftiofur administered to swine as the reformulated EXCENEL RTU EZ Sterile Suspension at a dose of 5 mg CE/kg BW by IM injection was demonstrated to be bioequivalent to a corresponding IM injection of EXCENEL RTU Sterile Suspension based upon comparability of their respective $AUC_{0\text{-}LOQ}$ and C_{max} values (see EFFECTIVENESS section). Because of the demonstrated blood level bioequivalence, this study confirms the systemic safety of the reformulated EXCENEL RTU EZ Sterile Suspension in swine when administered by IM injection at a dose of 5 mg CE/kg BW for three consecutive days.

Injection site tissue tolerance and resolution were evaluated after administering EXCENEL RTU EZ Sterile Suspension by intramuscular injection to 8 young pigs with at least the maximum proposed volume of 5 mL per injection site once daily for three consecutive days. Each injection was administered in a different location on the neck, and injection sites alternated between the left and right sides. General health and injection sites were evaluated through 42 days after the first treatment. No test article-related health issues were observed. Mild swelling, erythema, and firmness was observed in a very small number of occasions (≤ 2% of total observations). No swelling was observed from 3 days after the last injection through the end of the study. Grossly visible discoloration of the injection site and histopathologic changes consistent with inflammation were noted in treated pigs necropsied 7 days or 14 days after injection.

Cattle: Evaluation of target animal safety in cattle was based on two PK studies comparing the reformulated EXCENEL RTU EZ Sterile Suspension and EXCENEL RTU Sterile Suspension (one study comparing IM administration and one study comparing SC administration). In both studies, ceftiofur, when administered to cattle at a dose of 2.2 mg CE/kg BW of the reformulated EXCENEL RTU EZ Sterile Suspension, was demonstrated to be bioequivalent to a 2.2 mg CE/kg BW dose of EXCENEL RTU Sterile Suspension (see EFFECTIVENESS section). Because of the demonstrated blood-level bioequivalence, these studies confirm systemic safety of the reformulated EXCENEL RTU EZ Sterile Suspension when administered either IM or SC at a dose of 2.2 mg CE/kg BW for five consecutive days.

Injection site tissue tolerance and lesion resolution were evaluated after administration of the reformulated EXCENEL RTU EZ Sterile Suspension by intramuscular and subcutaneous injections to 16 growing cattle (8 cattle for each route) at the maximum volume of 15 mL per injection site, once daily for five consecutive days. Each injection was administered in a different location on the neck and injection sites alternated between the left and right sides. General health and injection sites were evaluated through necropsy (up to 42 days after the first dose). Animals were euthanized on Day 7, 14, 28, or 42 (two calves at each time point). No test article-related health issues were observed. Injection site reactions consisted of firmness and swelling at the injection sites. Injection site swelling was observed in 4/1030 (0.4%) of IM injection site observations and in 606/1029 (58.9%) of SC injection site observations. Swelling progressively decreased over time, and was still present in both animals injected SC that were necropsied on Day 42. Grossly visible discoloration of the injection site and/or histopathologic changes consistent with inflammation were noted through Day 42 in SC and IM injection sites.

TISSUE RESIDUE DEPLETION

Swine: Radiolabeled residue metabolism studies established tolerances for ceftiofur residues in swine kidney, liver and muscle. The tolerances for ceftiofur residues are 0.25 ppm in kidney, 3.0 ppm in liver and 2.0 ppm in muscle.

A pivotal tissue residue decline study was conducted in swine. In this study, pigs received 2.27 mg of ceftiofur per lb body weight (5 mg of ceftiofur per kg body weight) per day for three consecutive days. Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in tissues such as kidney and muscle by 4 days after dosing. These data collectively support a 4-day pre-slaughter withdrawal period in swine when used according to label directions.

Cattle: A radiolabeled residue metabolism study established tolerances for ceftiofur residues in cattle kidney, liver and muscle. A separate study established the tolerance for ceftiofur residues in milk. The tolerances for ceftiofur residues are 0.4 ppm in kidney, 2.0 ppm in liver, 1.0 ppm in muscle and 0.1 ppm in milk.

Two pivotal tissue residue decline studies were conducted in cattle. Cattle received either a subcutaneous injection or intramuscular injection of 1.0 mg of ceftiofur per lb body weight (2.2 mg per kg body weight). In both studies, ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in tissues such as the kidney and muscle by 4 days after dosing. These data collectively support a 4-day pre-slaughter withdrawal period when used according to label directions.

STORAGE CONDITIONS

Store at controlled room temperature 20° to 25°C (68° to 77°F); excursions permitted 15° to 40°C (59° to 104°F). Protect from freezing. Shake well before using. Contents should be used within 42 days after the first dose is removed.

HOW SUPPLIED

EXCENEL RTU EZ Sterile Suspension is available in 100 mL and 250 mL vials.

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