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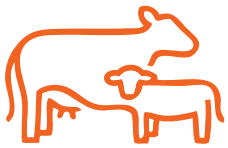
TECHNICAL BULLETIN

June 2018



Impacts of Dairy Cow Body Weight Variation on Correct Dosing of EXCEDE® and EXCENEL® RTU EZ

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To avoid expensive underdosing or overdosing of antimicrobials in lactating dairy cows, doses must be based on actual body weights, not crude set-doses.

Summary

- Two studies assessed the body weight variability of dairy cows at freshening, to generate insight regarding the risks of antimicrobial underdosing or overdosing if animals are treated at subjective set-doses instead of using actual body weight measurements.
  - 704 heifers/cows at a Wisconsin dairy were weighed on *digital scales* within 2 days of calving, with data categorized by lactation number (L1 n=300, L2 n=213, L3+ n=191).[1]
  - 420 heifers/cows from 42 Wisconsin dairies were measured using a *weight tape* within 2 days of calving, with data categorized by lactation number (L1 n=210, L2+ n=210).[2]
  - Correct doses of EXCEDE® and EXCENEL® RTU EZ appropriate for metritis treatment were determined for each cow, by lactation number.
- Large differences in body weight between lactations were observed. Body weight extremes within lactations were also large, ranging from 675 to 1245 lb.
- Most animals were at risk of underdosing or overdosing with EXCEDE or EXCENEL RTU EZ if set-doses were used instead of doses based on actual body weights (underdosed by up to 36% or overdosed by up to 43% compared to average calculated correct doses).
- Underdosing and overdosing pose potential adverse economic impacts through loss of productivity, increased treatment costs due to unresolved disease or relapse, or bulk tank contamination with residue-laden milk, and reflect poor antimicrobial stewardship.
- Dairy managers should consider amending calving/freshening protocols to include the capture of cow weight data with a weight tape (or scales if available) and dose antimicrobials based on actual body weight, not guess-based set-doses.

Recommended label dosages for antimicrobial medications reflect the outcomes of extensive research by drug developers, covering FDA-mandated aspects such as efficacy, residues, animal safety, reproductive safety, environmental impact, etc. Use of the labeled effective dose in sick, suffering animals is necessary to provide the best opportunity for disease resolution and return to productivity. Most commonly, antimicrobial dosages are based on animal body weight (BW), so the actual weight of an animal must be known to accurately treat the animal in an effective and safe manner.

Unfortunately, dairy producers often administer injectable antimicrobials using crude 'set-doses' based on subjective visual estimates of BW for 'large' and 'small' cows. This common practice fails to account for the broad range of BW within and across lactations, and thus may put a dairy at high risk of routinely underdosing or overdosing lactating cows with antimicrobials (e.g.,

Set-doses of anti-microbials based on subjective visual BW estimates fail to account for the broad weight range within and across lactations, thus risking routine under- or overdosing of lactating cows.

EXCEDE® and EXCENEL® RTU EZ offer the potent efficacy of ceftiofur for metritis treatment with no milk discard, but must be dosed correctly based on actual cow weights.

when treating an important, economically significant disease like metritis that can severely erode productivity). Such casual, ball-park estimates of dose rates may threaten income potential by jeopardizing the health, milk production, reproductive success, and residue status of the herd. For example, failure to visually detect a 100- or 200-lb difference between cows may mean a heavier animal is underdosed, receiving a dose too low for its BW. Antimicrobial efficacy may be compromised as a result, leading to poor treatment response and additional input costs of increased labor (to re-treat and handle animals), additional medications, or even use of other antibiotics with unknown withdrawal times. In contrast, overdosing a smaller animal that receives a dose too high for its BW can increase the risk of violative residues in milk or meat while wasting costly medicine. Management efforts aimed at ensuring accurate, BW-based antimicrobial treatment of lactating dairy cows can contribute toward optimizing operational productivity and profit potential.

Two studies were conducted to assess the BW variability of dairy cows at freshening, to generate insight regarding the risks of antimicrobial underdosing or overdosing if animals are treated at subjective set-doses instead of using accurate BW measurements. The context of these studies involved scenarios for treating acute post-partum metritis with ceftiofur (EXCEDE® and EXCENEL® RTU EZ), an antimicrobial widely used in lactating dairy cows because no milk discard is required.

EXCEDE® and EXCENEL® RTU EZ

EXCEDE Sterile Suspension (ceftiofur crystalline free acid) is the potent third-generation cephalosporin antimicrobial that offers excellent therapy for post-calving metritis in lactating dairy cattle as well as single-dose treatment of bovine respiratory disease (BRD) and foot rot. Dairy producers often prefer EXCEDE because it can be used with *no milk discard* (13-day pre-slaughter withdrawal). EXCEDE provides the demonstrated efficacy of ceftiofur in a convenient extended-therapy formulation designed for subcutaneous (SC) administration at the base of the ear in lactating dairy cows at a dose of 3 mg ceftiofur equivalents (CE) per lb BW (1.5 mL EXCEDE/100 lb BW). More recently, a 2-dose regimen of EXCEDE was approved for the treatment of acute metritis (0-10 days postpartum) in lactating dairy cows, with the same dose repeated in the opposite ear approximately 72 hours following the initial dose. This metritis indication represented a significant therapeutic advance for dairy veterinarians and their clients.

EXCENEL RTU EZ (ceftiofur hydrochloride) is another ceftiofur formulation approved, like EXCEDE, for the treatment of acute postpartum metritis, BRD, and foot rot in lactating dairy cows. EXCENEL RTU EZ is ready-to-use for injection via conventional SC or intramuscular sites, offering high efficacy with the confidence of *no milk discard* (and only a 4-day pre-slaughter withdrawal). For treatment of acute postpartum metritis, EXCENEL RTU EZ should be administered at the dosage of 1 mg CE per lb BW (2 mL EXCENEL RTU EZ/100 lb BW) at 24-hour intervals for 5 consecutive days (≤ 15 mL/injection site).

Experiment Design

Two separate field studies were conducted in Wisconsin to assess BW variation of dairy cows at freshening. The first study was conducted at a major commercial dairy where 704 cows were weighed on digital scales within 2 days of calving ('scales study').[1] Data were categorized for 3 groups of cows by lactation, involving 300 first-lactation heifers (L1), 213 second-lactation cows (L2), and 191 cows in their third lactation or beyond (L3+).

The second study measured 420 cows from 42 commercial dairies, where BW was captured using a weight tape within 2 days of calving ('weight tape study').[2] Data in this survey were categorized for 2 groups of cows by lactation, involving 210 L1 heifers and 210 L2+ cows in their second lactation or beyond.

In each study, descriptive BW data for the heifers/cows were calculated (mean, range, etc.) by lactation, and the correct doses of EXCEDE and EXCENEL RTU EZ appropriate for metritis treatment were determined.

Results — Scales study

Outcomes summarized in Figure 1 and Table 1 describe the BW demographics and variability of the herd by lactation categories. As expected, large BW variations across lactations were observed, with L1 heifers generally lighter in weight (avg. 1262 lb) while BW increased with lactation number (avg. 1552 lb for L2, 1749 lb for L3+). Within lactation, BW varied by 685, 680, and a massive 1245 lb for L1, L2, and L3+ cows, respectively.

Figure 2 and Table 1 show the number of cattle in each lactation relative to the number of mL of EXCEDE they should receive to be correctly treated for metritis

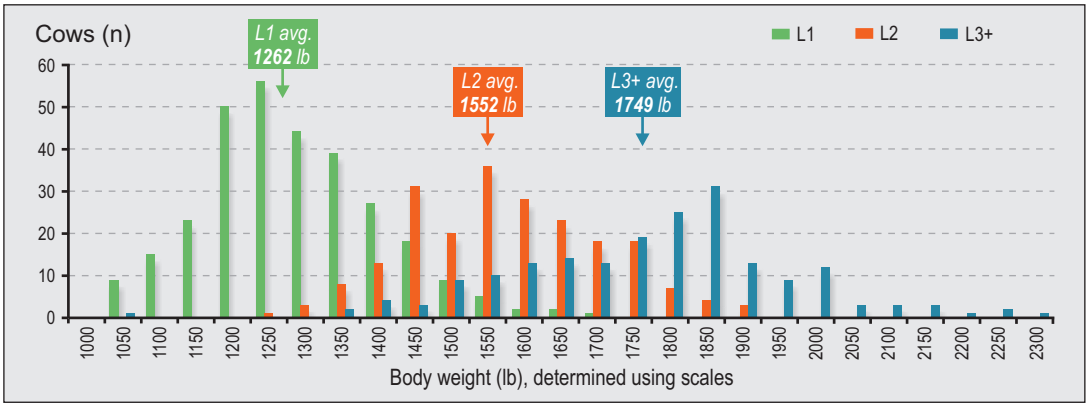


Figure 1 – *Scales:* Distribution of individual cow body weights measured at freshening using scales, by lactation number (1 dairy, n=704).

Large BW variations across lactations were observed, and cow weights within lactation varied by 680 to 1245 lb.

Table 1 – Scales study outcomes.

Parameter	Lactation 1	Lactation 2	Lactation 3+
Total cows (n)	300	213	191
Avg. weight (lb)	1262	1552	1749
Minimum (lb)	1010	1220	1020
Maximum (lb)	1695	1900	2265
Range (lb)	685	680	1245
EXCEDE correct dose/day (1.5 mL/100 lb BW)			
Avg. (mL)	19	23	26
Minimum (mL)	15	18	15
Overdose if avg. used	21%	22%	42%
Maximum (mL)	25	29	34
Underdose if avg. used	-32%	-26%	-31%
Range (mL)	10	11	19
EXCENEL RTU EZ correct dose/day (2 mL/100 lb BW)			
Avg. (mL)	25	31	35
Minimum (mL)	20	24	20
Overdose if avg. used	20%	23%	43%
Maximum (mL)	34	38	45
Underdose if avg. used	-36%	-23%	-29%
Range (mL)	14	14	25

Correct EXCEDE® dosages within lactation categories varied by 21% to 42% from the group average for the lightest-weight cows, and 26% to 32% for the heaviest cows.

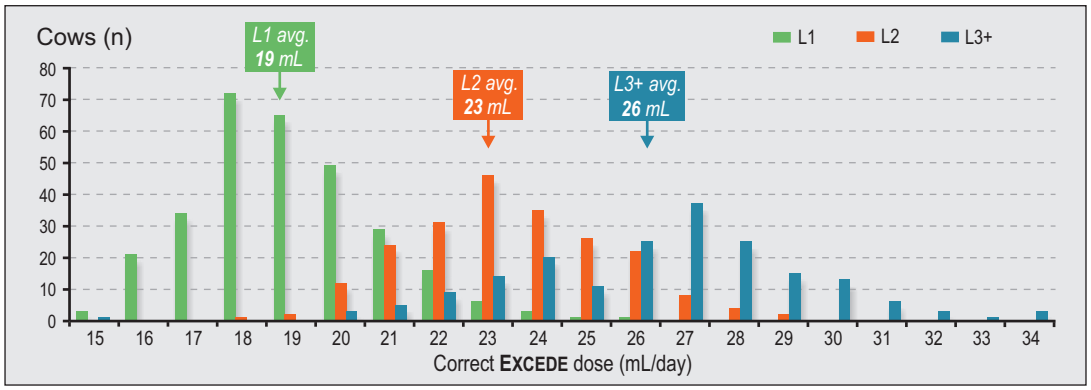


Figure 2 – *Scales:* Distribution of correct EXCEDE doses (mL/hd/d) based on BW of cows, by lactation number (metritis treatment requires 2-dose regimen at 72-h interval).

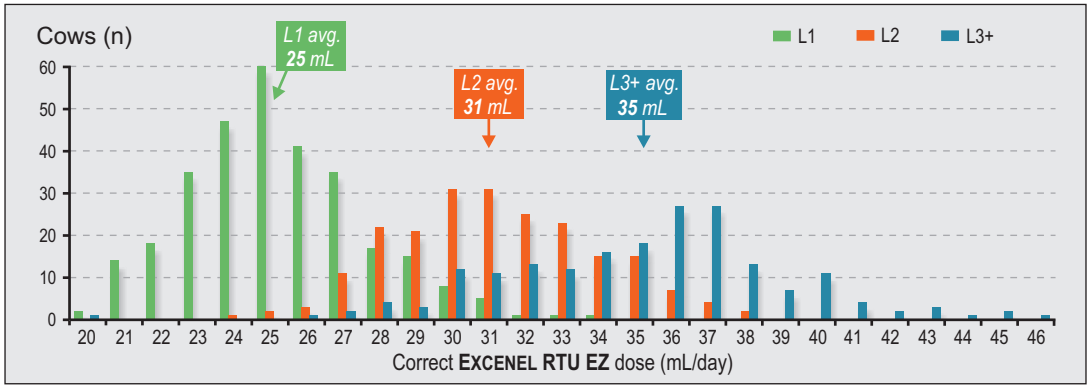


Figure 3 – *Scales:* Distribution of correct EXCENEL RTU EZ doses (mL/hd/d) based on BW of cows, by lactation number (metritis treatment requires 5-dose regimen at 24-h interval).

Correct EXCENEL® RTU EZ dosages within lactation categories varied by 20% to 43% from the group average for the lightest-weight cows, and 23% to 36% for the heaviest cows.

at the daily label dose rate of 1.5 mL/100 lb BW. The wide variations in BW were reflected by EXCEDE dose volumes, and the great range of mL needed for accurate metritis treatment without over- or underdosing is evident. Needed dosages within lactation categories varied by 21% to 42% from the group average for the lightest-weight cows, and 26% to 32% for the heaviest cows, clearly suggesting that even use of an average set-dose would result in severe overdosing or underdosing for a sizable portion of the herd. Similar outcomes for correct EXCENEL RTU EZ dosing (Figure 3 and Table 1; daily label dose rate of 2 mL/100 lb BW) show the lightest-weight cows getting overdosed by 20% to 43% and the heaviest cows getting underdosed by 23% to 36% compared to the average dose within lactations. Clearly, the potential for massive underdosing and overdosing in the absence of accurate BW-based dosing could severely impact drug efficacy and residue concerns, respectively.

Results — Weight tape study

The BW demographics and variability of cows involved in the weight tape study are summarized in Figure 4 and Table 2. Again, large BW variations across the 2 lactation categories were observed, with L1 heifers generally lighter in weight (avg. 1326 lb) while BW was greater in the L2+ group (avg. 1537 lb). Within lactation, a 675-lb variation range was observed for L1 animals, and the weight variation between animals in the L2+ group was even larger at 965 lb.

Data regarding the number of mL of EXCEDE that cows in each lactation should receive for metritis treatment (daily label dose rate of 1.5 mL/100 lb BW) are also presented in Table 2. Wide variations in BW were again reflected by variations of EXCEDE dose volumes needed for accurate metritis treatment without over- or underdosing. Correct dosages within lactation categories varied by 25% to 30% from the group average for both the

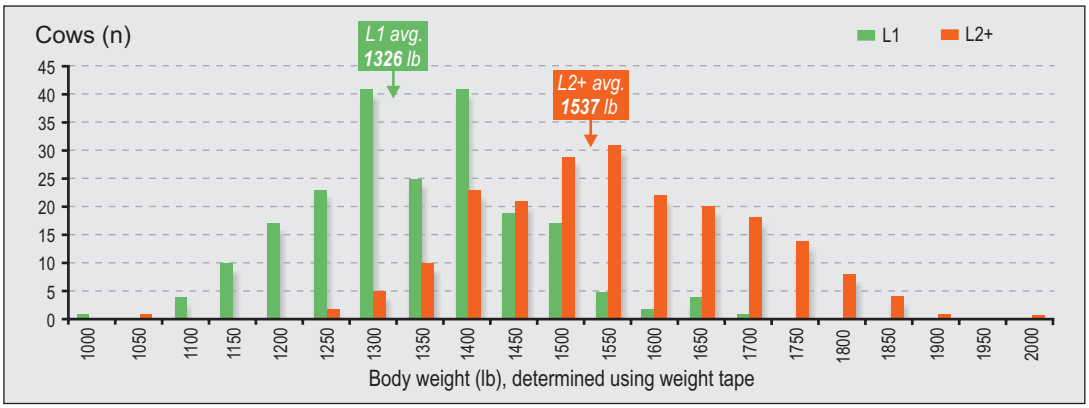


Figure 4 – *Weight tape:* Distribution of individual cow body weights measured at freshening using a weight tape, by lactation number (42 dairies, n=420).

Outcomes for the weight tape study were similar to the scales study: use of a set-dose would result in severe overdosing or underdosing for much of the cow herd.

Table 2 – Weight tape study outcomes.

Parameter	Lactation 1	Lactation 2+
Total cows (n)	210	210
Avg. weight (lb)	1326	1537
Minimum (lb)	1000	1035
Maximum (lb)	1675	2000
Range (lb)	675	965
EXCEDE correct dose/day (1.5 mL/100 lb BW)		
Avg. (mL)	20	23
Minimum (mL)	15	16
Overdose if avg. used	25%	30%
Maximum (mL)	25	30
Underdose if avg. used	-25%	-30%
Range (mL)	10	14
EXCENEL RTU EZ correct dose/day (2 mL/100 lb BW)		
Avg. (mL)	27	31
Minimum (mL)	20	21
Overdose if avg. used	26%	32%
Maximum (mL)	34	40
Underdose if avg. used	-26%	-29%
Range (mL)	14	19

lightest-weight and heaviest cows, clearly suggesting that even use of an average set-dose would result in severe overdosing or underdosing for much of the herd. Similar outcomes for correct EXCENEL RTU EZ dosing (Table 2; daily label dose rate of 2 mL/100 lb BW) indicate that some cows could be overdosed or underdosed by 26% or more compared to the average dose within lactations. Results of the weight tape study were very similar to those of the scales study, confirming the potential for massive underdosing and overdosing in the absence of accurate BW-based dosing.

Implications

Results of these studies investigating BW variation of dairy cows at freshening illuminate some of the consequences of using set, pre-determined doses of antimicrobials instead of dosing based on actual BW. Large BW variation clearly exists within herds and within lactations in herds, leading to high proportions of cows that might be underdosed or overdosed if treated according to set-doses instead of actual BW.

Underdosing of lactating cows suffering with metritis is likely to compromise antimicrobial efficacy and the prospects for disease resolution. If a lack of effectiveness is perceived, one of the first remedies would be to question whether the antimicrobial was accurately dosed based on actual BW instead of crude guesses of approximate animal size. These studies showed that the heaviest cows could be underdosed by 23% to 36% relative to the average dose needed for animals in the same lactation, and such underdosing would be expected to erode treatment response of any medication. Lack of efficacy due to underdosing increases input costs due to the need for additional labor and medication, in addition to the reduced milk production typical of sick cows.

If a lack of antimicrobial effectiveness is perceived, check whether the medication was accurately dosed based on actual BW instead of crude guesses of animal size.

Dairy managers should consider amending calving/ freshening protocols to include the capture of cow BW data.

Use of a weight tape offers a fast and easy method for obtaining critical BW information that can substantially improve the likelihood for positive medication outcomes.

Overdosing presents a whole other set of hazards, primarily related to residue concerns but also the fact that more antimicrobial might be used than needed, which obviously wastes funds used to purchase medication. In these studies, lightest-weight cows within a lactation would be overdosed by 20% to 43% relative to the average dose needed for cows in the same lactation. Such overdosing could certainly affect drug clearance from the cow and/or accumulation in the milk, potentially causing violative residues in the bulk tank.

Both underdosing and overdosing pose the potential for significant economic impacts, through loss of productivity and increased treatment costs due to unresolved disease or relapse, or bulk tank contamination with residue-laden milk. Such improper dosing also reflects poor antimicrobial stewardship and is incompatible with industry initiatives and goals advocating for judicious use of these critical production tools. Notably, more than half the number of cattle receiving antimicrobials on study dairies were unknowingly being overdosed or underdosed. Furthermore, the overdosing or underdosing potentials illustrated by study BW variations reflect outcomes based on a *single* daily dose. The potential for over/underdosing is greatly magnified and perpetuated by completion of the entire 2- or 5-dose regimens needed for EXCEDE and EXCENEL RTU EZ, respectively.

Study outcomes clarify the importance of capturing individual cow BW data at freshening by using a weight tape or digital cattle scale, and the need for dairy managers to stop guessing about cow BW when using antimicrobial treatment. At a minimum, the fast and easy collection of cow weight tape data should be added to calving/freshening protocols.

Conclusions

The common practice of using antimicrobial 'set-doses' based on visual BW estimates for large and small lactating cows can compromise drug efficacy, increase input costs, and elevate the potential for violative residues in milk. Study results demonstrated the large BW variability that exists in dairy herds, including animals in the same lactation. Use of a set-dose of antimicrobial instead of a dose based on actual individual BW can cause many animals in a herd to be significantly underdosed or overdosed, outcomes that can exert serious adverse economic impacts.

Prudent dairy managers should consider amending calving/freshening protocols to include the capture of cow BW data. If scales are not available, the use of a weight tape offers a fast and easy method for obtaining critical BW information that can substantially improve the likelihood for positive outcomes when treating lactating cows with EXCEDE, EXCENEL RTU EZ, or most any other medication. Contact a Zoetis Territory Business Manager for tools and insight that can help producers build a more strategic plan for proper dosing of antimicrobials.

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

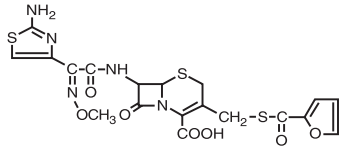
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Federal Law prohibits extra-label use of this drug in cattle for disease prevention purposes; at unapproved doses; frequencies, durations, or routes of administration; and in unapproved major food producing species/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

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.

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

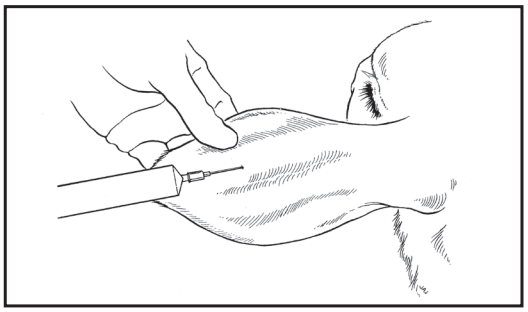
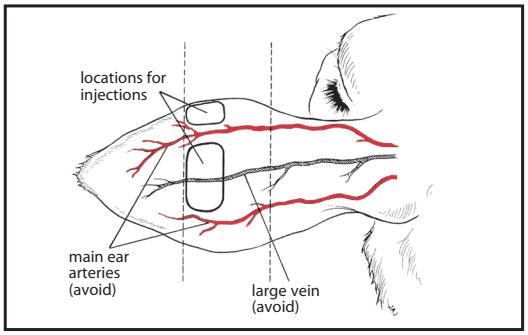


Figure 3. Diagram of the approximate locations of the major arteries of the posterior ear and the recommended needle insertion locations. Administration of EXCEDE Sterile Suspension into ear arteries is likely to be fatal.



ADMINISTRATION FOR 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.

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).

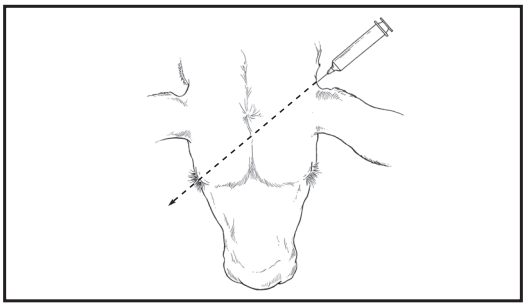
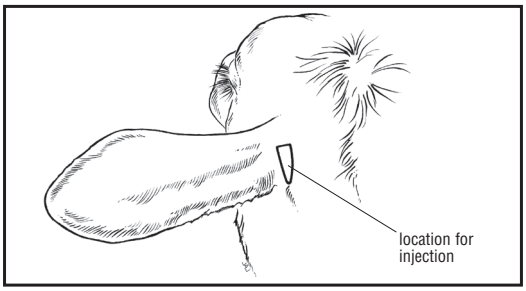


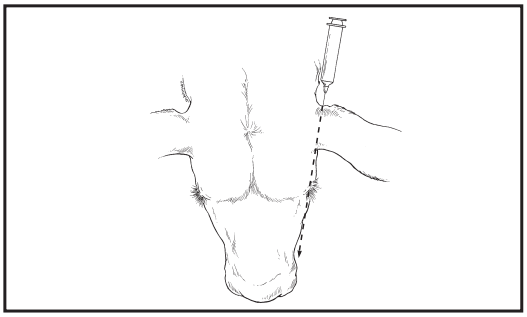
Figure 5. Injection location for the subcutaneous administration of EXCEDE Sterile Suspension in the posterior aspect of the ear where it attaches to the head (base of the ear).



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.

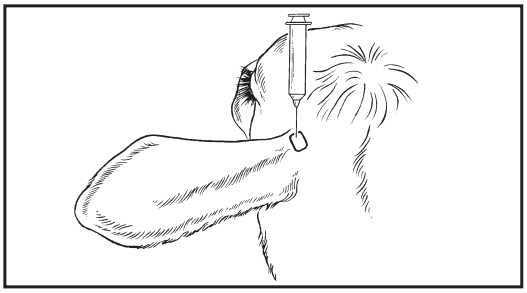
Figure 6. Diagram of head showing the direction for the base of ear injections administered rostrally toward the eye on the same side of the head into the loose skin in the caudal aspect of the base of the ear.



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

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 towards 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.**

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 where 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 towards 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.

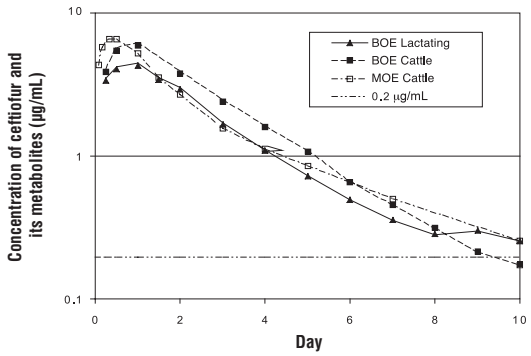


Table 2. Average (n = 12/group) pharmacokinetic parameters for ceftiofur and desfuroylceftiofur metabolites calculated after a single subcutaneous administration of 3.0 mg CE/lb (6.6 mg CE/kg) BW of EXCEDE Sterile Suspension in either the middle third of the ear or the base of the ear.

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
$AUC_{0\text{-}LOQ}$ (µg•h/mL)	376 ± 66.1	412 ± 67.3	313 ± 85.5
$t_{>0.2,\ model}$ (h)	183 ± 40.8	NE	NE
$t_{>0.2,\ nca}$ (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).
$AUC_{0\text{-}LOQ}$ (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).
$t_{>0.2,\ model}$ (h) = the time plasma concentrations remain above 0.2 µg CE/mL (in hours), estimated using compartmental pharmacokinetic techniques.
$t_{>0.2,\ nca}$ (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.

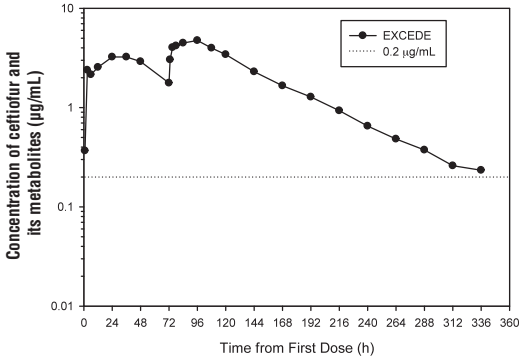


Table 3. Average (n = 12) Pharmacokinetic Parameters Following Two Subcutaneous Injections of EXCEDE Sterile Suspension at a Dose 3.0 mg CE/lb (6.6 mg CE/kg) BW at a 72 Hour Interval.

PK Parameter	Mean ± Standard Deviation
$AUC_{0\text{-}LOQ}$ (µg•h/mL)	651 ± 119
$t_{½}$ (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) BW 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, approximately 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 the oil-based 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 decline 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 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

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

www.EXCEDE.com or call 1-888-963-8471

Revised: August 2013

10423902A&P

EXCENEL® RTU EZ

(*ceftiofur hydrochloride*)
Sterile Suspension

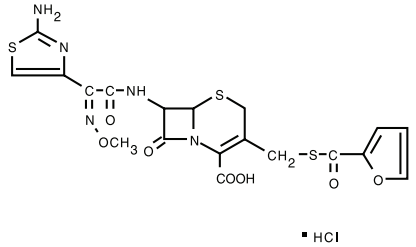
For intramuscular injection in swine. For intramuscular and subcutaneous injection in cattle. This product may be used in lactating dairy cattle. Not for use in calves to be processed for veal.

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:



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.

NADA 141-288, Approved by FDA

Revised: March 2013

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

References

1. Data on file, Wisconsin dairy scale study. Zoetis LLC.
2. Data on file, Wisconsin dairy weight tape study. Zoetis LLC.

TAKE TIME
OBSERVE LABEL DIRECTIONS

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