EXCENEL® RTU EZ
Ceftiofur Hydrochloride
Sterile Suspension

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.

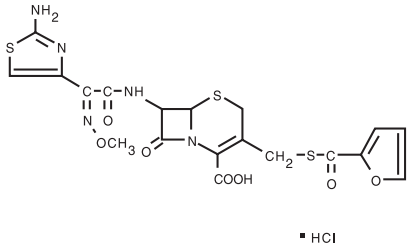
CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Federal law prohibits extra-label use of this drug in cattle for disease prevention purposes; at unapproved doses, frequencies, durations, or routes of administration; and in unapproved major food producing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

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)]]-

Figure 1. Structure:



INDICATIONS

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.

— 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 safety data sheet contains more detailed occupational safety information. To obtain a safety data sheet (SDS) 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:

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 reproductive performance, pregnancy and lactation have not been determined.

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

CLINICAL PHARMACOLOGY

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 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 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 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 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 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

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

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

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 ppm in liver, 1 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 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.

Approved by FDA under NADA # 141-288

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Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007