

EXCENEL[®] RTU EZ

Ceftiofur Hydrochloride

Sterile Suspension



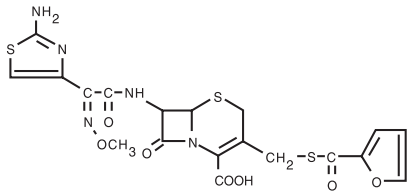
For intramuscular injection in swine.

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 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 suspension.

Figure 1. Structure:



• HCl

Chemical Name of Ceftiofur Hydrochloride: 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[[2-amino-4-thiazolyl](methoxyimino)-acetyl]amino]-3-[[[2-(furan-2-carbonyl)thio]methyl]-8-oxo-5-hydroxy]-8-oxo-1,8-dihydro-1,2,4-triazolo[4,3-c]pyridine-6-carboxylic acid hydrochloride salt [6R-[6a,7b(2Z)]]

INDICATIONS

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 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:

Injection site volume affects the withdrawal period in swine. When used according to label indications, dosage, and route of administration, treated swine must not be slaughtered for 6 days following the last treatment when injection site volumes are greater than 5 mL up to the maximum injection site volume of 15 mL. When used according to label indications, dosage, and route of administration, treated swine must not be slaughtered for 4 days when injection site volumes are less than or equal to 5 mL. **Do not inject more than 15 mL per injection site.** Use of dosages or injection volumes in excess of those indicated or by unapproved routes of administration may result in illegal residues in edible tissues.

PRECAUTIONS

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

Intramuscular injection in swine 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 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 MIC₉₀ for *Salmonella Choleraesuis* (1 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 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 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 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 ₀₋₁₀₀ (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
 AUC₀₋₁₀₀ - 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, AUC₀₋₁₀₀ and C_{max}, when each formulation was administered to swine IM at a dose rate of 2.27 mg CE/lb (5 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 AUC₀₋₁₀₀ in swine following an IM administration of 2.27 mg CE/lb (5 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 ₀₋₁₀₀ | 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 mg CE/kg) BW). The bioequivalence criteria were met for the AUC₀₋₁₀₀, C_{max}, and t_{0.2}. When both products were administered by an intramuscular injection to swine at a dose rate of 5 mg CE/kg BW.

The effectiveness of injection site volumes greater than 5 mL to 15 mL was supported by a comparison of the length of time (hours) that plasma concentrations remained above 0.2 µg/mL (t_{0.2}) between injection site volumes less than or equal to 5 mL and injection site volumes greater than 5 mL to 12 mL. Statistical analysis allowed for an extrapolation of these findings to 15 mL per site. The pharmacokinetic data demonstrated that 5 mg/kg administered IM at injection volumes from greater than 5 mL to 15 mL resulted in acceptable t_{0.2} for the indication.

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 melanogenicus*, pathogenic anaerobic bacteria associated with bovine foot rot.

Utilizing data that included isolates from swine 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 |
| <i>Actinobacillus pleuropneumoniae</i> <i>Pasteurella multocida</i> <i>Salmonella Choleraesuis</i> | 30 µg | ≥ 21 | 18 to 20 | ≤ 17 | ≤ 2.0 | 4.0 | ≥ 8.0 |
| <i>Mannheimia haemolytica</i> <i>Pasteurella multocida</i> <i>Histophilus somni</i> | | | | | | | |

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 administration in swine were compared and found to be bioequivalent for AUC₀₋₁₀₀ 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.

ANIMAL SAFETY

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 AUC₀₋₁₀₀ 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.

A second injection site tissue tolerance study was conducted in 16 adult commercial crossbred pigs to evaluate the administration of EXCENEL RTU EZ Sterile Suspension by intramuscular injection with a maximum dose volume of 15 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. No swelling, erythema, or firmness were observed during the study. Gross necropsy and histopathologic changes consistent with inflammation were noted in treated pigs necropsied up to 42 days after injection.

TISSUE RESIDUE DEPLETION

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 ppm in liver and 2 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 with an injection volume of 5 mL per site. Ceftiofur residues in edible tissues were less than the tolerances for ceftiofur at 4 days after dosing.

A second pivotal tissue residue decline study was conducted in large swine. In this study, animals received 3 consecutive once daily doses of EXCENEL RTU EZ Sterile Suspension by intramuscular injection at a dose rate of 2.27 mg of ceftiofur per lb body weight (5 mg CE/kg BW) with a maximum injection volume of 15 mL per injection site. Ceftiofur residues in tissues were below the tolerance in kidney by 6 days after dosing.

Collectively, the data from these two studies support a 4-day pre-slaughter withdrawal period in swine receiving injection site volumes less than or equal to 5 mL and a 6-day withdrawal period when receiving injection site volumes greater than 5 mL up to 15 mL per injection site.

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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