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 any further transfer of this drug by retail or other than retail establishments.

**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 of ceftiofur, 1.8% polyethylene glycol 400, 4,2-(2-amino-4-thiazolyl)(methoxyimino)-acetyl alcohol, 7-[2-[[amino-4-fluorophenyl]acetyl]amino]-6-chloro-3-carboxylic acid, and 0.05% hydrochloric acid (HCl).

**INDICATIONS**

EXCENEL RTU EZ Sterile Suspension is indicated for the 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
- Acute metritis (0 to 14 days post-partum) associated with bacterial organisms susceptible to ceftiofur
- Acute metritis (0 to 14 days post-partum) associated with bacterial organisms susceptible to ceftiofur

**DOSE AND ADMINISTRATION**

Shake well before use.

- 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 (not required after the fifth administration) in the event of treatment failure, however, for BMR only, administer intramuscularly or subcutaneously 1 mg CE/lb (2.2 mg CE/kg) BW every other day on Day 1, and 3 (7 to 9 hour intervals). Do not inject more than 10 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 should be avoided. Use of these products includes the potential for severe allergic reactions in some individuals. Repeated exposure or prolonged exposure may lead to sensitization. Avoid direct contact of the product with the skin, eyes, mouth, and clothing.

Penicillins with a known hypersensitivity to penicillin or cephalosporins should avoid exposure to this product.

In case of accidental exposure, wash 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 immediately.

The safety data sheet contains more detailed occupational safety information. To obtain a safety data sheet (SDS) or to determine compatibility with food contact surfaces, contact the manufacturer or the distributor.

**RESIDUE WARNINGS:**

When used according to label indications, dosage and route of administration, treated cattle must not be slaughtered for food for at least 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 extra-label uses 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.

**CAUTION:** 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 EFSA/EFSA section). Because of the demonstrated 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. Injection site tissue tolerance and lesion resolution were not affected by use of the reformulated EXCENEL RTU EZ Sterile Suspension compared to the standard formulation, EXCENEL RTU EZ Sterile Suspension.

**CONTRAINDICATIONS**

The effects of ceftiofur on cattle reproductive performance, pregnancy and lactation have not been determined. Tissue and fluid distribution were less than the tolerances for ceftiofur residues in tissues such as the kidney and muscle by 4 days after treatment.

**ANIMAL SAFETY**

- The standard bioequivalence (BE) criteria, based upon the exponentiated 90% confidence bounds about the ratio of pharmacokinetic parameters, were met for the pivotal bioequivalence parameters, AUC, and Cmax when each formulation 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).

**MATERIAL**

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 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 (M3-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.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Disk potency</th>
<th>Zone diameter interpretive standards (mm)</th>
<th>MIC breakpoint (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinobacillus pleuropneumoniae</td>
<td>S</td>
<td>18 to 20</td>
<td>2.0</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
<td>S</td>
<td>18 to 20</td>
<td>2.0</td>
</tr>
<tr>
<td>Salmonella Choleraesuis</td>
<td>S</td>
<td>18 to 20</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*These interpretive criteria are only intended for use when CLSI M3-A2 performance standards are used to determine antimicrobial susceptibility.

**EFFECTIVENESS**

The bioequivalence of ceftiofur as administered as EXCENEL RTU Sterile Suspension or as EXCENEL RTU EZ Sterile Suspension has not been established for cattle following an IM and SC administration of 1 mg CE/lb (2.2 mg CE/kg) BW. Any such evaluation would be in accordance with the provisions of 21 CFR 514.126, 514.128, and 514.130 for new animal drug submissions. Furthermore, because the bioavailability of ceftiofur following an IM administration of 1 mg CE/lb (2.2 mg CE/kg) BW has not been established, the bioavailability of ceftiofur following an SC administration of 1 mg CE/lb (2.2 mg CE/kg) BW has not been evaluated.

**ANIMAL SAFETY**

- A radiolabeled metabolism study was conducted to establish equilibrium for ceftiofur residues in cattle kidney, liver and muscle. A separate study established the tolerances for ceftiofur residues in milk. The tolerances for ceftiofur residues are 6.4 μg/kg in kidney, 2 ppm in liver, 1 ppm in muscle and 0.1 ppm in milk. Two intramuscular or subcutaneous injections of 1 mg of ceftiofur per lb bodyweight were administered in cattle. Cattle received either a subcutaneous or intramuscualar injection of 1 mg of ceftiofur per lb body weight (2.2 mg per kg body weight). In both studies, ceftiofur residues were established to be 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. Store 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

**Table 3:** Comparative treatment values (arithmetic mean ± SD) for the plasma PK estimates of total ceftiofur (parent compound plus desacetyl 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).

**Table 4:** Table-transformed least squares (LS) and 90% confidence intervals (CI) for the two pivotal pharmacokinetic parameters, AUC, and Cmax 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).

**Figure 1:** Structure: