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 ceftiofur hydrochloride equivalent to 50 mg ceftiofur in a caprylic/capric triglyceride (Miglyol® 812) injection site.

INDICATIONS EXCENEL RTU EZ Sterile Suspension is indicated for treatment of the following bacterial diseases:
- Bovine respiratory disease (BRD), shipping fever, pneumonia associated with Actinobacillus pleuropneumoniae, Pasteurella multocida, Salmonella Cholerasuis and Streptococcus suis.
- Acute bovine interdigital necrobacillosis (foot rot, pododermatitis) caused by Bacteroides melaninogenicus and Bacteroides fragilis.
- Acute metritis (0 to 14 days post-partum) associated with bacterial organisms susceptible to ceftiofur.

DOSAGE AND ADMINISTRATION

Shake well before use. 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 contains 22.7 mg CE/kg BW). Administration 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, adminiser 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 at 4 day intervals after ceasing clinical signs 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 the disease, pathogen susceptibility and clinical response.

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 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.

RESIDUE WARNINGS:

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: For at least 4 days following treatment, 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 lowest minimum inhibitory concentration to encompass 90% of the most sensitive bacterial isolates (MICS) for several swine BRD pathogens Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni.

Cmax - maximum plasma concentration
AUC0-LOQ - the area under the plasma concentration vs. time curve from time of injection to the limit of quantification of the assay
Cmax - the time after initial injection to which Cmax occurs
t1/2 - the plasma half life of the drug
Cmin - the time plasma concentrations remain above 0.2 μg/mL

PK Parameter LS Mean Difference 90% CI Beta

Cmax (μg/mL) 1.19 1.03 to 1.18 Yes
AUC0-LOQ (μg*h/mL) 263 ± 54.8 263 ± 54.8
AUC0-LOQ 1.03 0.99 to 1.06 Yes

Table: 2 Back-transformed least squares (LS) means and 90% confidence interval (CI) for the two pivotal pharmacokinetic parameters, Cmax and AUC0-LOQ in swine following an IM administration of 2.27 mg CE/kg BW, as either EXCENEL RTU (reference article) or as EXCENEL RTU EZ Sterile Suspension (test article).

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 a recent 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 approved dose range (2.27 mg CE/kg (5.0 mg CE/kg) BW). The bioequivalence criteria were met for the AUC0-LOQ and Cmax, when both products were administered by an intramuscular injection to a swine at a dose rate of 5.0 mg CE/kg BW.

Cattle: Cattle 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 MIC90 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 MIC90, and in plasma for long periods of time after a single IM administration for at least 48 hours. The relationship between plasma concentrations of ceftiofur and desfuroylceftiofur metabolites above the MIC90, and in plasma for long periods of time after a single IM administration for at least 48 hours.

PK Parameter LS Mean Difference 90% CI Beta

Cmax (μg/mL) 6.58 ± 1.50 5.91 ± 1.37 Yes
AUC0-LOQ (μg*h/mL) 86.4 ± 13.6 86.7 ± 10.3 91.0 ± 20.2

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/kg BW, as either EXCENEL RTU (reference article) or as EXCENEL RTU EZ Sterile Suspension (test article).

Cmax - maximum plasma concentration
AUC0-LOQ - the area under the plasma concentration vs. time curve from time of injection to the limit of quantification of the assay
Cmax - the time after initial injection to which Cmax occurs
AUC0-LOQ - the plasma half life of the drug
Cmin - 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-LOQ and Cmax, when each formulation was administered to cattle IM or SC at a dose rate of 1.0 mg CE/kg (2.2 mg CE/kg) BW (Table 4).

Table: 4 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/kg BW, as either EXCENEL RTU (reference article) or as EXCENEL RTU EZ Sterile Suspension (test article).
Table 4: Back-transformed least squares (LS) means and 90% confidence intervals (CI) for the two pivotal pharmacokinetic parameters, \(C_{\text{max}}\) 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).

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>IM</th>
<th>SC</th>
<th>IM LS Mean Difference</th>
<th>IM 90% CI</th>
<th>SC LS Mean Difference</th>
<th>SC 90% CI</th>
</tr>
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<tbody>
<tr>
<td>(C_{\text{max}})</td>
<td>1.08</td>
<td>1.00 to 1.16</td>
<td>1.09</td>
<td>1.02 to 1.18</td>
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<tr>
<td>AUC(_{0-\text{LOQ}})</td>
<td>0.984</td>
<td>0.94 to 1.03</td>
<td>1.06</td>
<td>0.98 to 1.13</td>
<td></td>
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</tbody>
</table>

In another comparative bioavailability PK study (previously reviewed under NADA 141-288), 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 0.5 mg to 1.0 mg CE/lb (1.1 to 2.2 mg CE/kg) BW.

**Mycrobiology**

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 Acinetobacter pleuropneumoniae, Pasteurella multocida, and Salmonella Choleratexis, three pathogens associated with swine respiratory disease. Similarly, in vitro activity of ceftiofur has been demonstrated against Mannheimia haemolytica, Pasteurella multocida, and Histophilus somni, three of the 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 with the three major pathogens associated with swine respiratory disease, zone diameter and minimum inhibitory 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.

**Pharmacokinetics Comparison**

To confirm the systemic safety of the reformulated EXCENEL RTU EZ Sterile Suspension in swine when administered by IM injection at a dose of 5.0 mg CE/kg BW for three consecutive days.

In a pivotal PK 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. 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 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 the 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°C to 25°C (68° to 77°F); excursions permitted 15°C 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.