Suitability Petition: Generic Ceftiofur Hydrochloride Sterile Suspension

P&U submits this petition under Section 512 (n)(3) of the Federal Food Drug and Cosmetic Act to request that the Commissioner of the FDA permit the filing of an ANADA for a generic copy of ceftiofur hydrochloride sterile suspension for use in cattle and swine as approved under NADA 140-890, EXCENEL® RTU brand of ceftiofur hydrochloride sterile suspension for intramuscular and subcutaneous use in cattle and for intramuscular injection in swine.

Action Requested: P&U requests FDA's permission to submit an ANADA for a generic version of ceftiofur hydrochloride sterile suspension. The need for this petition arises from P&U's request for one change to the proposed label for this ANADA. The change proposed by P&U is to limit the route of administration for cattle to only the subcutaneous route instead of both subcutaneous and intramuscular as currently approved under NADA 140-890. No other changes are proposed for the label for this proposed generic product.

Pioneer Product:

Trade Name: EXCENEL® RTU brand of ceftiofur hydrochloride sterile suspension (NADA 104-890)

Active Ingredient: Ceftiofur Hydrochloride

Dosage Form and Strength: A ready-to-use sterile suspension of ceftiofur hydrochloride containing 50 mg of ceftiofur equivalents per mL of suspension.

Sponsor: Pharmacia & Upjohn Company, A Division of Pfizer Inc.

Indications:

Swine: EXCENEL RTU Sterile Suspension is indicated for the treatment of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus (Hemophilus) pleuropneumoniae, Pasteurella multocida, Salmonella choleraesuis,* and *Sterptococcus suis* type 2.

Cattle: EXCENEL RTU 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 *Hemophilus somnus.*
- Acute bovine interdigital necrobacillosis (foot rot, pododermititis) associated with *Fusobacterium necrophorum* and *Bacteroides melaniongenicus.*
- Acute metritis (0-14 days postpartum) associated with bacterial organism susceptible to ceftiofur.

Dosage and Administration:

Swine: Administer intramuscularly at a dosage of 1.36 to 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) BW (1 mL of sterile suspension to 22-37 lb BW). Treatment should be repeated at 24 h intervals for three consecutive days.

Cattle:

- For bovine respiratory disease and acute bovine interdigital necrobacillosis: administer by intramuscular or subcutaneous administration at a dosage of 0.5 to 1.0 mg ceftiofur equivalents/lb (1.1 to 2.2 mg/kg) BW (1 to 2 ml sterile suspension per 100 lb BW). Administer daily at 24 h intervals for a total of three consecutive days. Additional treatment 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 1.0 mg ceftiofur equivalents (2.2 mg/kg) BW every other day on days 1 and 3 (48 h interval). Do not inject more than 15 mL per injection site.

  Selection of dosage levels (0.5 to 1.0 mg/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 postpartum metritis: administer by intramuscular or subcutaneous administration at the dosage of 1.0 mg of ceftiofur equivalents/lb (2.2 mg/kg) BW (2 mL sterile suspension per 100 lb BW). Administer at 24-hour intervals for five consecutive days; do not inject more that 15 mL per injection site.

Proposed Drug Product

Trade Name: to be determined

Active Ingredient: Ceftiofur Hydrochloride

Dosage Form and Strength: A ready to use sterile suspension of ceftiofur hydrochloride containing 50 mg of ceftiofur equivalents per mL of suspension.

Sponsor: Pharmacia & Upjohn Company, A Division of Pfizer Inc.

Indications:

Swine: EXCENEL RTU Sterile Suspension is indicated for the treatment of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus (Hemophilus) pleuropneumoniae, Pasteurella multocida, Salmonella choleraesuis,* and *Sterptococcus suis* type 2.

Cattle: EXCENEL RTU 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 *Hemophilus somnus.*

- Acute bovine interdigital necrobacillosis (foot rot, pododermititis) associated with *Fusobacterium necrophorum* and *Bacteroides melaniongenicus.*

- Acute metritis (0-14 days postpartum) associated with bacterial organism susceptible to ceftiofur.

Dosage and Administration:

Swine: Administer intramuscularly at a dosage of 1.36 to 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) BW (1 mL of sterile suspension to 22-37 lb BW). Treatment should be repeated at 24 h intervals for three consecutive days.

Cattle:

- For bovine respiratory disease and acute bovine interdigital necrobacillosis: administer by subcutaneous administration at a dosage of 0.5 to 1.0 mg ceftiofur equivalents/lb (1.1 to 2.2 mg/kg) BW (1 to 2 ml sterile suspension per 100 lb BW). Administer daily at 24 h intervals for a total of three consecutive days. Additional treatment 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 subcutaneously 1.0 mg ceftiofur equivalents (2.2 mg/kg) BW every other day on days 1 and 3 (48 h interval). Do not inject more than 15 mL per injection site.

  Selection of dosage levels (0.5 to 1.0 mg/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 postpartum metritis: administer by subcutaneous administration at the dosage of 1.0 mg of ceftiofur equivalents/lb (2.2 mg/kg) BW (2 mL sterile suspension per 100 lb BW). Administer at 24-hour intervals for five consecutive days do not inject more that 15 mL per injection site.

Statement of Grounds: The proposed generic copy will utilize the same active as the pioneer product in new sterile suspension. As previously noted except for the restriction to the subcutaneous route of injection in cattle, the remainder of the label will be identical to the pioneer product. The justification for this change is that the cattle industry has moved away from intramuscular injection and for this reason, P&U is proposing removal of the intramuscular route from the proposed generic product.

Environmental Impact: P&U requests a categorical exclusion from the requirement to file an environmental assessment for this ANADA as noted in 21 CFR 25.33 (a) (1). As noted in 21 CFR 25.21, we know of no extraordinary circumstances that exist for this proposed ANADA.

Economic Impact: P&U will submit economic information if requested by FDA.

Label Comparison: A copy of the approved EXCENEL RTU labeling is found in **Attachment 1.** For the proposed ANADA, the word intramauscular will be removed from all appropriate sections of the letter including: the product header, cattle portions of the Dosage and Administration, Precaution sections of product labeling. The product name, ANADA number, product number and suspension excipients will change but these should be expected with an ANADA approval.

Certification: P&U certifies that this suitability petition contains all information known to the company that is unfavorable to the petition.

John W. Hallberg, D.V.M., PhD.
Associate Director Regulatory Affairs.

Date: 7 June 2005

RECEIVED
JUN 28 2005

NDC 0009-3504-03 100 mL

EXCENEL® RTU

Sterile Suspension

ceftiofur hydrochloride sterile suspension

Equivalent to

50 mg per mL

ceftiofur

For intramuscular and subcutaneous injection in cattle and intramuscular injection in swine.

This Product May Be Used In Lactating Dairy Cattle.

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Restricted Drug—Use Only As Directed (California)

For Use in Animals Only

NADA #140-890, Approved by FDA

Swine	1.36 - 2.27 mg/lb	1mL/22 - 37 lb
Cattle	0.5 - 1.0 mg/lb	1mL/50 - 100 lb

For Once Daily Injection — See Package Insert

Warning: Not for human use Keep out of reach of children. To avoid possible allergic reactions, users are advised to avoid direct contact of this product with the skin or other mucous membranes. See package insert for complete product information.

RESIDUE WARNINGS

Swine: Treated swine must not be slaughtered for 4 days following the last treatment.

Cattle: Treated cattle must not be slaughtered for 2 days following the last treatment because unsafe levels of drug remain at the injection sites. No milk discard time is required when this product is used according to label directions. 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

Store at controlled room temperature 20° to 25° C (68° to 77° F) [see USP].

Protect from freezing.

Each mL contains: ceftiofur hydrochloride equivalent to 50 mg ceftiofur (0.50 mg phospholipon, 1.5 mg sorbitan monooleate, 2.25 mg sterile water for injection, and cottonseed oil). **Shake well before using.** U.S. Patent Nos. 4,902,683; 5,738,151

816 250 107B

Pharmacia &Upjohn

Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA

PHARMACIA Black PMS 877

Composition Unit 2566

COMPOSITION ORDER #	PRODUCT		COPY CODE #
22150	Excenel RTU		816 250 107B
CCS # 3504-03	NDC #	EDP # 691682	ITEM Label
BOTTLE #	SIZE 6.125 x 2"	IMPRINT SIZE .6875 x 2"	DRAWING # PD1211
ADDITIONAL INFORMATION Varnish All EXCEPT For The Imprint Area		DATE 10/06/03	TYPESET BY L. Amos

Pantone® colors used in this proof may not match the Pantone® solid color standards. Use current Pantone® swatch guide for most accurate color.

Excenel® RTU

Pharmacia
&Upjohn

brand of ceftiofur hydrochloride sterile suspension

For intramuscular and subcutaneous use in cattle and intramuscular use in swine. This product may be used in lactating dairy cattle.

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian

DESCRIPTION

EXCENEL RTU 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, 0 50 mg phospholipon, 1 5 mg sorbitan monooleate, 2 25 mg sterile water for injection and cottonseed oil

Structure

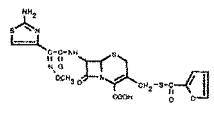

Figure 1

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)]]

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 MIC_{90} for the labeled pathogens *Actinobacillus pleuropneumoniae Pasteurella multocida Streptococcus suis* and *Salmonella choleraesuis* for the 24 hour (h) 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) body weight (BW) dose

Comparative Bioavailability Summary

Comparable plasma concentrations of ceftiofur administered as ceftiofur hydrochloride sterile suspension (EXCENEL RTU Sterile Suspension) or ceftiofur sodium sterile solution (NAXCEL® Sterile Powder) were demonstrated after intramuscular administration of 2 27 mg ceftiofur equivalents/lb (5 0 mg/kg) BW See Table 1 and Figure 2

Table 1. Swine plasma concentrations and related parameters* of ceftiofur and desfuroylceftiofur metabolites after EXCENEL RTU Sterile Suspension (ceftiofur hydrochloride sterile suspension, 50 mg/mL) or NAXCEL Sterile Powder (ceftiofur sodium sterile powder 50 mg/mL) administered at 2 27 mg/lb ceftiofur equivalents/lb (5 0 mg/kg) BW IM

	Ceftiofur hydrochloride	Ceftiofur sodium
C_{max} µg/mL	39 1 ± 5 02	29 2 ± 5.01
t_{max} h	0 66 – 2 0 (range)	0 33 – 2 0 (range)
AUC_{0-LOQ} µg•h/mL	321 ± 50.2	314 ± 55 1
$t_{1/2}$ h	16 2 ± 1 55	14 0 ± 1 23
$C_{24\,h}$ µg/mL	3 45 ± 0 431	3 53 ± 0 781
$C_{72\,h}$ µg/mL	0 518 ± 0 126	0 407 ± 0 0575
$t_{>0.2}$ h	93 8 ± 7 98	85 0 ± 7.71

Definitions.

C_{max} – maximum plasma concentration in µg/mL

t_{max} – the time after initial injection to when C_{max} occurs measured in hours

AUC_{0-LOQ} – the area under the plasma concentration vs time curve from time of injection to the limit of quantitation of the assay (0 15 µg/mL)

$t_{1/2}$ – the plasma half life of the drug in hours

$C_{24\,h}$ – the concentration of drug at 24 h after administration

$C_{72\,h}$ – the concentration of drug at 72 h after administration

$t_{>0.2}$ – the time (in hours) plasma concentrations remain above 0 2 µg/mL

* Due to significant period effect and significant sequence effect in this study, data from period 1 only were used to evaluate these parameters

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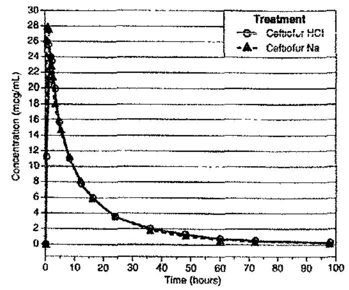
brand of ceftiofur hydrochloride sterile suspension

Figure 2. Swine plasma concentrations of ceftiofur and desfuroylceftiofur metabolites after EXCENEL RTU Sterile Suspension (ceftiofur hydrochloride sterile suspension, 50 mg/mL) or NAXCEL Sterile Powder (ceftiofur sodium sterile powder, 50 mg/mL) were administered intramuscularly at 2 27 mg ceftiofur equivalents/lb (5 0 mg/kg) BW



Concentrations of total ceftiofur in the lungs of pigs administered radiolabeled ceftiofur at 2 27 or 3 41 mg ceftiofur equivalents/lb (5 0 or 7 5 mg/kg) BW 12 h after the last of three daily intramuscular injections at 24 h intervals averaged 3 66 and 5 63 µg/g

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 bovine respiratory disease (BRD) label pathogens *Mannheimia haemolytica Pasteurella multocida* and *Haemophilus somnus* for at least 48 h The relationship between plasma concentrations of ceftiofur and desfuroylceftiofur metabolites above the MIC_{90} in plasma and efficacy has not been established for the treatment of bovine interdigital necrobacillosis (foot rot) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*

Comparative Bioavailability Summary

The comparability of plasma concentrations of ceftiofur following administration of ceftiofur hydrochloride sterile suspension (EXCENEL RTU Sterile Suspension) or ceftiofur sodium sterile solution (NAXCEL Sterile Powder) was demonstrated after intramuscular or subcutaneous administration of ceftiofur hydrochloride and intramuscular administration of ceftiofur sodium at 1 0 mg ceftiofur equivalents/lb (2 2 mg/kg) BW See Table 2 and Figure 3

Table 2. Cattle plasma concentrations and related parameters of ceftiofur and desfuroylceftiofur metabolites after EXCENEL RTU Sterile Suspension (ceftiofur hydrochloride sterile suspension, 50 mg/mL) administered intramuscularly or subcutaneously at 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW and NAXCEL Sterile Powder (ceftiofur sodium sterile powder, 50 mg/mL) administered intramuscularly at 1 0 mg ceftiofur equivalents/lb (2 2 mg/kg) BW

	Ceftiofur hydrochloride		Ceftiofur sodium
	IM	SC	IM†
C_{max} µg/mL	11 0 ± 1 69	8 56 ± 1 89	14 4–16 5
t_{max} h	1–4 (range)	1–5 (range)	0 33–3 0
$t_{>0.2}$ h	60.5 ± 6 27	51 0 ± 6 53	50 7–50 9
AUC_{0-LOQ} µg•h/mL	180 ± 30 7	95 4 ± 17 8	115–142
$t_{1/2}$ h	12 0 ± 2 93	11.5 ± 2 57	9 50–11 1
$C_{24\,h}$ µg/mL	1 47 ± 0 380	0 926 ± 0 257	0 86–1 16
$C_{48\,h}$ µg/mL	0 340 ± 0 110	0 271 ± 0 086	0 250–0 268

Definitions.

C_{max} – maximum concentration of drug in plasma in µg/mL

t_{max} – the time after initial injection to when C_{max} occurs, measured in hours

$t_{>0.2}$ – the time (in hours) plasma drug concentrations remain above 0 2 µg/mL

AUC_{0-LOQ} – the area under the plasma drug concentration vs. time curve from time of injection to the limit of quantitation of the assay (0 15 µg/mL)

$t_{1/2}$ – the drug half life in plasma expressed in hours

$C_{24\,h}$ – the plasma drug concentration 24 h after administration

$C_{48\,h}$ – the plasma drug concentration 48 h after administration

† Values represent the separate means from each study

Figure 3. Cattle plasma concentrations of ceftiofur and desfuroylceftiofur metabolites after administration of 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW of EXCENEL RTU Sterile Suspension (ceftiofur hydrochloride sterile suspension 50 mg/mL) by intramuscular or sub-

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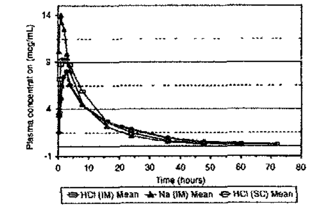
cutaneous injection or NAXCEL Sterile Powder (ceftiofur sodium sterile powder 50 mg/mL) by intramuscular injection



Total residues of ceftiofur were measured in the lungs of cattle administered radiolabeled ceftiofur at 1 0 mg ceftiofur equivalents/lb (2 2 mg/kg) BW at 24 h intervals for five consecutive days. Twelve h after the fifth injection of ceftiofur hydrochloride, total ceftiofur concentrations in the lung averaged 1 15 µg/g, while total ceftiofur concentrations in the lung 8 h after the fifth ceftiofur sodium injection averaged 1 18 µg/g

CLINICAL MICROBIOLOGY

EXCENEL RTU Sterile Suspension is a ready to use formulation that contains the hydrochloride salt of ceftiofur which is a broad spectrum cephalosporin antibiotic active against gram positive and gram-negative bacteria including β-lactamase-producing strains. Like other cephalosporins ceftiofur is bactericidal *in vitro*, resulting in inhibition of cell wall synthesis.

Swine. Studies with ceftiofur have demonstrated *in vitro* and *in vivo* activity against gram-negative pathogens including *Actinobacillus (Haemophilus) pleuropneumoniae, Pasteurella multocida Salmonella choleraesuis*, and the gram positive pathogen *Streptococcus suis* type 2 all of which can be associated with swine bacterial respiratory disease – SRD (swine bacterial pneumonia) A summary of the minimum inhibitory concentration (MIC) values from SRD pathogens isolated from clinical field effectiveness studies is found in Table 3 Historic diagnostic laboratory MIC values for SRD pathogens from the US and Canada are found in Table 4

Cattle Studies with ceftiofur have demonstrated *in vitro* and *in vivo* activity against *Mannheimia haemolytica Pasteurella multocida* and *Haemophilus somnus* the three major pathogenic bacteria associated with bovine respiratory disease (BRD, pneumonia, shipping fever), and against *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*, two of the major pathogenic anaerobic bacteria associated with acute bovine interdigital necrobacillosis (foot rot, pododermatitis) A summary of the MIC values for BRD and foot rot pathogens isolated from clinical field effectiveness studies is found in Table 3 Historic diagnostic MIC values for BRD and foot rot pathogens from the US and Canada are found in Table 4

Antimicrobial Susceptibility

Summaries of MIC data are presented in Tables 3 and 4 Testing followed NCCLS Guidelines (National Committee for Clinical Laboratory Standards)

Table 3 Ceftiofur MIC Values of Bacterial Isolates from Clinical Field Studies in the USA

Animal	Organism	Number Tested	Date Tested	MIC_{90}* (µg/mL)	MIC Range (µg/mL)
Bovine					
	Mannheimia haemolytica	461	1988–1992	0 06	<0 03-0 13
	Mannheimia haemolytica	42	1993	0.015	≤0.003–0.03
	Pasteurella multocida	318	1988–1992	0 06	<0 03–0 25
	Pasteurella multocida	48	1993	≤0.003	≤0.003–0.015
	Haemophilus somnus	109	1988–1992	0 06	≤0.03–0 13
	Haemophilus somnus	59	1993	≤0 0019	no range
	Fusobacterium necrophorum	17	1994	≤0 06	no range
Swine					
	Actinobacillus pleuropn	83	1993	<0 03	≤0 03–0 06
	Pasteurella multocida	74	1993	≤0 03	≤0.03–0.06
	Streptococcus suis	94	1993	0 25	≤0.03–1 0
	Salmonella choleraesuis	50	1993	1 0	1 0–2 0
	beta-hemolytic *Streptococcus spp*	24	1993	≤0 03	≤0 03–0 06
	Actinobacillus suis	77	1998	0 0078	0.0019-0.0078
	Haemophilus parasuis	76	1998	0.06	0 0039–0.25

*Minimum inhibitory concentration (MIC) for 90% of the isolates

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Table 4 Ceftiofur MIC Values of Bacterial Isolates from Diagnostic Laboratories* in the USA and Canada

Animal	Organism	Number Tested	Date Tested	MIC_{90}** (µg/mL)	MIC Range (µg/mL)
Bovine					
	Mannheimia haemolytica	110	1997–1998	0 06	≤0 03–0.25
	Mannheimia haemolytica	139	1998–1999	<0 03	≤0 03–0 5
	Mannheimia haemolytica	209	1999–2000	≤0 03	≤0 03–0 12
	Mannheimia haemolytica	169	2000–2001	≤0 03	≤0.03–0 12
	Pasteurella multocida	107	1997–1998	≤0 03	≤0 03–0.25
	Pasteurella multocida	181	1998–1999	≤0 03	≤0 03–0 5
	Pasteurella multocida	208	1999–2000	≤0 03	≤0 03–0 12
	Pasteurella multocida	259	2000–2001	≤0 03	≤0 03–0 12
	Haemophilus somnus	48	1997–1998	≤0 03	≤0.03–0.25
	Haemophilus somnus	87	1998–1999	≤0 03	≤0 03–0 125
	Haemophilus somnus	77	1999–2000	≤0 03	≤0 03–0.06
	Haemophilus somnus	129	2000–2001	≤0.03	≤0 03–0 12
	Bacteroides fragilis group	29	1994	16 0	≤0.06–>16 0
	Bacteroides spp., non-*fragilis* group	12	1994	16 0	0 13–>16 0
	Peptostreptococcus anaerobius	12	1994	2 0	0.13–2.0
Swine					
	Actinobacillus pleuropn	97	1997–1998	≤0 03	no range
	Actinobacillus pleuropn	111	1998–1999	≤0 03	≤0 03–0.25
	Actinobacillus pleuropn	126	1999–2000	≤0 03	≤0.03–0 06
	Actinobacillus pleuropn	89	2000–2001	≤0 03	≤0 03–0 06
	Pasteurella multocida	114	1997–1998	<0 03	≤0 03–1 0
	Pasteurella multocida	147	1998–1999	≤0 03	≤0 03–0 5
	Pasteurella multocida	173	1999–2000	≤0 03	≤0 03–0 06
	Pasteurella multocida	186	2000–2001	≤0 03	≤0.03–0 12
	Streptococcus suis	106	1997–1998	0 5	≤0 03–4.0
	Streptococcus suis	142	1998–1999	0.25	≤0 03 1 0
	Streptococcus suis	146	1999–2000	0 06	≤0.03–4 0
	Streptococcus suis	167	2000–2001	0.06	≤0 03–4 0
	Salmonella choleraesuis	96	1999–2000	1 0	0.03–>4 0
	Salmonella choleraesuis	101	2000–2001	1 0	0.5–2 0

* The following *in vitro* data are available but their clinical significance is unknown
** Minimum inhibitory concentration (MIC) for 90% of the isolates

Based on the pharmacokinetic studies of ceftiofur in swine and cattle after a single intramuscular injection of 1 36 to 2 27 mg ceftiofur equivalents/lb (3 0 to 5 0 mg/kg) BW (swine) or 0.5 to 1 0 mg ceftiofur equivalents/lb (1 1 to 2.2 mg/kg) BW (cattle) and the MIC and disk (30 µg) diffusion data the following breakpoints are recommended by NCCLS

Zone Diameter (mm)	MIC (µg/mL)	Interpretation
≥ 21	≤ 2 0	(S) Susceptible
18-20	4 0	(I) Intermediate
≤ 17	≥ 8 0	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels A report of "Intermediate" is a technical buffer zone and isolates falling into this category should be retested Alternatively the organism may be successfully treated if the infection is in a body site where drug is physiologically concentrated. A report of "Resistant" indicates that the achievable drug concentrations are unlikely to be inhibitory and other therapy should be selected

Standardized procedures† require the use of laboratory control organisms for both standardized diffusion techniques and standardized dilution techniques The 30 µg ceftiofur sodium disk should give the following zone diameters and the ceftiofur sodium standard reference powder (or disk) should provide the following MIC values for the reference strain Ceftiofur sodium disks or powder reference standard is appropriate for both ceftiofur salts

7

Composition Unit 2566

COMPOSITION ORDER #	PRODUCT			COPY CODE #
24154	EXCENEL RTU			816 323 310
COB # 3504-03	NDC #	EOP # 692431	ITEM Insert	
BOTTLE #	SIZE 20 x 10"	FOLDED SIZE 2 5 x 1 25"	DRAWING # PD2178 Rev 1	
ADDITIONAL INFORMATION		DATE 06/23/04	TYPESET BY KL/DHUFF	

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brand of ceftiofur hydrochloride sterile suspension

Table Acceptable quality control ranges for ceftiofur against National Committee for Clinical Laboratory Standards recommended American type Culture Collection (ATCC) reference strains

Organism name (ATCC No.)	Zone diameter* (mm)	MIC range (µg/mL)
Escherichia coli (25922)	26–31	0.25–1.0
Staphylococcus aureus (29213)	—	0.25–1.0
Staphylococcus aureus (25923)	27–31	—
Pseudomonas aeruginosa (27853)	14–18	16.0–64.0
Actinobacillus pleuropneumoniae (27090)	34–42**	0.004–0.015***
Haemophilus somnus (700025)	36–46**	0.0005–0.004***

* All testing performed using a 30 µg disk

** Quality control ranges are applicable only to tests performed by disk diffusion test using a chocolate Mueller Hinton agar incubated in 5.7% CO_2 for 20-24 hours.

*** MIC quality control ranges are applicable only to tests performed by broth microdilution procedures using veterinary fastidious medium (VFM)

CLINICAL EFFICACY

Cattle: In addition to demonstrating comparable plasma concentrations, the following clinical efficacy data are provided

A clinical study was conducted to evaluate the efficacy of ceftiofur hydrochloride administered subcutaneously for the treatment of the bacterial component of BRD under natural field conditions. When uniform clinical signs of BRD were present, 60 cattle (131 to 207 kg) were randomly assigned to one of the following treatment groups: negative control or ceftiofur hydrochloride at 0.5 or 1.0 ceftiofur equivalents/lb (1.1 or 2.2 mg/kg) BW. Treatments were administered daily for three consecutive days. Cattle were evaluated daily and animals that died or were euthanatized were necropsied and the lung lesions scored. On Day 15, all surviving animals were euthanatized and necropsied and the lung lesions scored. Mortality rates were 65%, 10% and 5% for negative controls, 0.5 mg ceftiofur equivalents/lb and 1.0 mg ceftiofur equivalents/lb, (1.1 or 2.2 mg/kg) BW, respectively. Mortality rates for both ceftiofur hydrochloride treatment groups were lower than for negative controls ($P \leq 0.0001$). Rectal temperatures 24 h after third treatment were 104.0°F, 103.1°F and 102.3°F for negative controls, 0.5 mg/lb and 1.0 mg/lb (1.1 or 2.2 mg/kg) BW, respectively. The temperatures for both ceftiofur hydrochloride treatment groups were lower than the negative controls ($P \leq 0.05$). Ceftiofur hydrochloride administered subcutaneously for three consecutive days at 0.5 or 1.0 mg ceftiofur equivalents/lb (1.1 or 2.2 mg/kg) BW is an effective treatment for the bacterial component of BRD

A three location clinical field study was conducted to evaluate the efficacy of ceftiofur hydrochloride administered intramuscularly daily for three days or every other day (Days 1 and 3) for the treatment of the bacterial component of naturally occurring BRD. When uniform signs of BRD were present, 360 beef crossbred cattle were randomly assigned to one of the following treatment groups: negative control, ceftiofur sodium at 0.5 mg ceftiofur equivalents/lb (1.1 mg/kg) BW daily for three days, ceftiofur hydrochloride at 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW daily for three days, or ceftiofur hydrochloride at 1.0 mg ceftiofur equivalents/lb BW on Days 1 and 3 (every other day). All treatments were administered intramuscularly. All ceftiofur treatment groups (hydrochloride and sodium) and treatment regimens (every day and every other day) significantly ($P \leq 0.05$) reduced Day 4 rectal temperatures as compared to the negative control. Clinical success on Days 10 and 28 and mortality to Day 28 were not different for the ceftiofur groups (hydrochloride and sodium) and treatment regimens (every day and every other day). The results of this study demonstrate that daily and every other day (Days 1 and 3) intramuscular administration of ceftiofur hydrochloride are effective treatment regimens for the bacterial component of BRD

An eight location study was conducted under natural field conditions to evaluate the efficacy of ceftiofur hydrochloride for the treatment of acute post-partum metritis (0 to 14 days post-partum). When clinical signs of acute post-partum metritis (rectal temperature ≥ 103°F and fetid vaginal discharge) were observed, 361 lactating dairy cows were assigned randomly to treatment or negative control. Cattle were dosed either subcutaneously or intramuscularly daily for five consecutive days. On days 1, 5 and 9 after the last day of dose administration, cows were evaluated for clinical signs of acute post partum metritis. A cure was defined as rectal temperature < 103°F and lack of fetid discharge. Cure rate for the 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW dose group was significantly improved relative to cure rate of the negative control on day 9. The results of this study demonstrate that ceftiofur hydrochloride administered daily for five consecutive days at a dose of 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW is an effective treatment for acute post-partum metritis.

ANIMAL SAFETY

Swine: Results from a five-day tolerance study in normal feeder pigs indicated that ceftiofur sodium was well tolerated when administered at 57 mg ceftiofur equivalents/lb (125 mg/kg) (more than 25 times the highest recommended daily dosage of 2.27 mg/lb (5.0 mg/kg)) BW for five consecutive days. Ceftiofur administered intramuscularly to pigs produced no overt adverse signs of toxicity.

To determine the safety margin in swine, a safety-toxicity study was conducted. Five barrows and five gilts per group were administered ceftiofur sodium intramuscularly at 0, 2.27, 6.81 and 11.36 mg ceftiofur equivalents/lb (0, 5, 15, 25 mg/kg) BW for 15 days. This is 0, 1, 3 and 5 times the highest recommended dose of 2.27 mg/lb (5.0 mg/kg) BW/day and 5 times the recommended treatment length of 3 days. There were no adverse systemic effects observed, indicating that ceftiofur has a wide margin of safety when injected intramuscularly into feeder pigs at the highest recommended dose of 2.27 mg ceftiofur equivalents/lb (5.0 mg/kg) BW daily for 3 days or at levels up to 5 times the highest recommended dose for 5 times the recommended length of treatment.

A separate study evaluated the injection site tissue tolerance of EXCENEL RTU (ceftiofur hydrochloride) in swine when administered intramuscularly in the neck at 1.36 and 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) BW. Animals were necropsied at intervals to permit evaluations at 12 h and 3, 5, 7, 9, 11, 15, 20 and 25 days after last injection. Injection

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sites were evaluated grossly at necropsy. No apparent changes (swelling or inflammation) were observed clinically after 12 h post-injection. Areas of discoloration associated with the injection site were observed at time periods less than 11 days after last injection.

Cattle: Results from a five-day tolerance study in feeder calves indicated that ceftiofur sodium was well tolerated at 25 times (25 mg ceftiofur equivalents/lb, 55 mg/kg, BW) the highest recommended dose of 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW for five consecutive days. Ceftiofur administered intramuscularly 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, 5, 5 and 10 times the highest recommended dose of 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW to determine the safety factor. There were no adverse systemic effects indicating that ceftiofur sodium has a wide margin of safety when injected intramuscularly into the feeder calves at 10 times (10 mg ceftiofur equivalents/lb, 22 mg/kg, BW) the recommended dose for three times (15 days) the recommended length of treatment of three to five days. Local tissue tolerance to intramuscular injection of ceftiofur hydrochloride was evaluated in the following study.

Results from a tissue tolerance study indicated that ceftiofur hydrochloride was well tolerated and produced no systemic toxicity in cattle when administered intramuscularly in the neck and rear leg at a dose of 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW at each injection site. This represents a total dose per animal of 2.0 mg ceftiofur equivalents/lb (4.4 mg/kg) BW. Clinically noted changes (local swelling) at injection sites in the neck were very infrequent (2/48 sites) whereas noted changes in rear leg sites were more frequent (21/48 sites). These changes in the rear leg injection sites were generally evident on the day following injection and lasted from 1 to 11 days. At necropsy, injection sites were recognized by discoloration of the subcutaneous tissues and muscle that resolved in approximately 7 to 15 days in the neck and 19 to 28 days in the rear leg.

Results from another tissue tolerance study indicated that ceftiofur hydrochloride was well tolerated and produced no systemic toxicity to cattle when administered subcutaneously at 0.5 or 1.0 mg ceftiofur equivalents/lb (1.1 or 2.2 mg/kg) BW at 24 h intervals for 5 days. Mild and usually transient, clinically visible or palpable reactions (focal swelling) were localized at the injection site. At necropsy, injection sites were routinely recognized by edema, limited increase in thickness and color changes of the subcutaneous tissue and/or fascial surface of underlying muscle. The fascial surface of the muscle was visibly affected in most cases through 9.5 days after injection. Underlying muscle mass was not involved. There were no apparent differences in tissue response to administration of ceftiofur hydrochloride at 0.5 or 1.0 mg ceftiofur equivalents/lb (1.1 or 2.2 mg/kg) BW.

INDICATIONS

Swine: EXCENEL RTU Sterile Suspension is indicated for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus (Haemophilus) pleuropneumoniae, Pasteurella multocida, Salmonella choleraesuis* and *Streptococcus suis* type 2.

Cattle: EXCENEL RTU 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 *Haemophilus somnus.*

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.

CONTRAINDICATIONS

As with all drugs, the use of EXCENEL RTU Sterile Suspension is contraindicated in animals previously found to be hypersensitive to the drug.

DOSAGE AND ADMINISTRATION

Shake well before using

Swine: Administer intramuscularly at a dosage of 1.36 to 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) BW (1 mL of sterile suspension per 22 to 37 lb BW). Treatment should be repeated at 24 h intervals for a total of three consecutive days.

Cattle:

For bovine respiratory disease and acute bovine interdigital necrobacillosis, administer by intramuscular or subcutaneous administration at the dosage of 0.5 to 1.0 mg ceftiofur equivalents/lb (1.1 to 2.2 mg/kg) BW (1 to 2 mL sterile suspension per 100 lb BW). Administer daily at 24 h 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 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW every other day on Days 1 and 3 (48 h intervals). Do not inject more than 15 mL per injection site.

Selection of dosage level (0.5 to 1.0 mg/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 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW (2 mL sterile suspension per 100 lb BW). Administer at 24 h intervals for five consecutive days. Do not inject more than 15 mL per injection site.

WARNINGS

NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN

Restricted Drug (California) — Use Only As Directed

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) please call 1-800 733-5500. To report any adverse event please call 1-800-366 5288.

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Tissue Residue Depletion

Swine: Radiolabeled residue metabolism studies established tolerances for ceftiofur residues in swine kidney, liver, and muscle. These tolerances of 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, liver 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.

RESIDUE WARNINGS.

Swine: 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 may result in illegal residues in edible tissues.

Cattle: Treated cattle must not be slaughtered for 2 days following the last treatment because unsafe levels of drug remain at the injection site. No milk discard time is required when this product is used according to label directions. Use 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

Swine: Areas of discoloration associated with the injection site at time periods of 11 days or less may result in trim-out of edible tissues at slaughter. The safety of ceftiofur has not been demonstrated for pregnant swine or swine intended for breeding.

Cattle: Following intramuscular or subcutaneous administration in the neck, areas of discoloration at the site may persist beyond 11 days resulting in trim loss of edible tissues at slaughter. Following intramuscular administration in the rear leg, areas of discoloration at the injection site may persist beyond 28 days resulting in trim loss of edible tissues at slaughter.

STORAGE CONDITIONS

Store at controlled room temperature 20 to 25°C (68 to 77°F) [see USP]. Shake well before using. Protect from freezing.

HOW SUPPLIED

EXCENEL RTU Sterile Suspension is available in the following package size:

100 mL vial — NDC 0009-3504-03

[1] National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals. Approved Standard – Second Edition. NCCLS document M31-A2. NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, 2002.

NADA #140-890, Approved by FDA

U.S. Patent Nos. 4,902,683; 5,736,151

Pharmacia — Upjohn Company • Kalamazoo, MI 49001, USA

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816-323-310
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3504-03-000

Pfizer

Composition Unit 2566

COMPOSITION ORDER #	PRODUCT		COPY CODE #
241154	EXCENEL RTU		816 323 310
CCS #	NDC #	EDP #	ITEM
3504-03		692431	Insert
BOTTLE #	SIZE	FOLDED SIZE	DRAWING #
	20 x 10"	2.5 x 1.25"	PD2175 Rev 1
ADDITIONAL INFORMATION		DATE	TYPESET BY
		06/23/04	KL/DHUFF

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