MANAGING THE COSTS AND IMPACT OF METRITIS IN DAIRY COWS

Metritis, one of the most common fresh cow diseases, can be costly to the health of individual cows and the overall productivity of dairy operations, especially in today's environment. Fortunately with diligent monitoring of fresh cows, combined with early diagnosis, timely and effective intervention, the health, productivity and economic impacts of metritis can be reduced.

MEASURING THE SCOPE AND ECONOMICS OF METRITIS

Metritis is a uterine infection that affects about 20% of lactating dairy cows, although the incidence can range from 5% to more than 40% of cows in some herds. Typically seen within the first 10 days in milk (DIM), metritis is characterized by a foul-smelling, reddish-brown, watery vaginal discharge and systemic signs of illness such as decreased feed intake and milk production, with or without fever. It can range from a mild infection that a healthy cow can clear without intervention to a severe, life-threatening disease.

The costs associated with metritis can be substantial. Metritis can lower a cow's milk production, decrease fertility and future pregnancy rates, put her at greater risk of culling, and increase labor and treatment costs. One key reproductive parameter contributing to increased costs is prolonged time from calving to breed-back. This can be affected by postpartum conditions such as metritis during the first 30 DIM and subclinical or clinical endometritis, an inflammation of the endometrium (innermost uterine lining) that occurs during 31 to 60 DIM. As a result, metritis is estimated to cost producers between $329 and $386 per cow.[1] Although metritis cannot be completely prevented, its costly consequences can be minimized. Cows with metritis should be identified early and appropriately treated to reduce the disease's effects and return cows to reproductive health and production as effectively and quickly as possible.

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MONITORING STRATEGIES HELP DETECT ISSUES EARLY

Early detection followed by appropriate intervention is key to successfully treating any disease. For dairies, that means closely monitoring fresh cows for clinical signs and symptoms of metritis. Since metritis often follows calving complications such as retained placenta, dystocia, twins or stillbirths, these cows in particular should be monitored closely for metritis signs.

Fresh cows should be observed at least twice daily for a minimum of 10 days, and preferably for 14 days, after calving. When checking fresh cows, you or your employees should check both the front and back of each fresh cow. The following steps can help identify cows with metritis or another fresh-cow health problem:

- **Evaluate uterine/vaginal discharge.** Cows normally can have an odorless, red to brownish-red (mostly bloody) vaginal discharge for up to 14 days after calving. But a fetid-smelling, reddish-brown to gray discharge is a sign of an infection or retained placenta.
- **Check rectal temperature for fever.** While a fever greater than 103 degrees Fahrenheit can be a telltale sign of a health problem, be aware that as many as 60% of cows with metritis don't have an elevated temperature. (Normal rectal temperature for dairy cows ranges from 100.4 to 102.8 degrees Fahrenheit.)
- **Assess manure consistency.** Manure should be firm enough to form a patty. However, foul-smelling manure with a fluid consistency or that contains blood may indicate disease or a poorly functioning rumen.
- **Look for cows with a decreased appetite.** Check for the absence of feed "holes" in front of cows after they've been at the feed bunk to identify those that are standing at the bunk but not eating.
- **Check udder fill before milking and milk weights daily or at every milking.** Milk yield and udder fill can provide clues about a cow's overall health and how it has been eating. An udder that isn't full can be a sign that the cow may be experiencing metritis, ketosis, hypocalcemia (milk fever), displaced abomasum or pneumonia.
- **Assess the cow's appearance and demeanor.** Watch for signs of general depression such as standing alone, lack of appetite and low hanging head. Sunken eyes can suggest dehydration, while crusty eyes and nasal discharge can indicate a potential respiratory problem. Cold, droopy ears also may indicate a sick cow, possibly one with low blood calcium (hypocalcemia). And don't forget to check tail position since a raised tailhead can be a sign of uterine inflammation.

If you suspect a cow has metritis, have your veterinarian evaluate the cow to confirm your suspicions with a diagnosis. Cows with metritis typically can stay in the fresh pen and don't need to be moved to a hospital pen unless the case is complicated.

TREAT EARLY TO REDUCE DISEASE IMPACTS AND RETURN FRESH COWS TO PRODUCTION

Once a diagnosis of metritis is confirmed, prompt treatment with a systemic antibiotic is appropriate to return the cow to health and peak productivity. Cefenil® RTU (ceftiofur hydrochloride) sterile suspension from Norbrook Laboratories is now approved by the Food and Drug Administration for use in lactating dairy cows to treat acute metritis associated with ceftiofur-susceptible bacteria. It's also approved for treatment of foot rot and bovine respiratory disease caused by susceptible bacteria.

The first ready-to-use, veterinary-prescription, generic ceftiofur hydrochloride injectable, Cefenil RTU is easy to incorporate into your existing fresh cow monitoring and disease treatment protocols. To treat metritis, administer Cefenil RTU subcutaneously or intramuscularly at a dosage of 2 mL sterile suspension per 100 pounds of body weight once every 24 hours for five consecutive days. When treatment timing coincides with one of the fresh cow evaluations, you or your employees have an opportunity to assess treated cows and confirm whether they're improving or if they need additional supportive care.

With Cefenil RTU, there's zero milk discard, so milking routines aren't disrupted. There's also no need to move cows to hospital pens which can add stress to an already-stressed cow. The injectable suspension's three-day preslaughter withdrawal is one of the shortest withdrawal times for treatments on the market today.

The bottom line is that Cefenil RTU provides you and your herd with the same effective treatment as Excenel® RTU EZ but as a more cost-effective formula.

Cefenil RTU is made by Norbrook Laboratories, a company committed to producing generic veterinary pharmaceutical products. Norbrook is known for providing quality medicines, economical pricing of its products and its commitment to enhancing the health of food and companion animals. To learn more about Cefenil RTU, contact your Norbrook representative, call (866) 591-5777 or visit us online at Norbrook.com.

A VETERINARIAN'S PERSPECTIVE: MANAGING METRITIS IN THE DAIRY

For Dr. David Chapman, a veterinarian with Stateline Veterinary Services in Darien, Wi., managing metritis is a serious condition that can impact 5 to 10% of the producing dairy cows in their service area. "It's a high-impact disease that we need to pay attention to that pops up from time to time. And it's one that cost producers not only in lost milk production and fewer days in milk, but also lost reproductive capacity and production over the life of the cow."

Stateline Veterinary Services was one of the first practices to use Cefenil RTU when it was introduced and Dr. Chapman says it's been highly effective in helping them and their producers treat metritis. "The active ingredient in Cefenil RTU has a great track record in treating metritis-causing bacteria that are sensitive to ceftiofur hydrochloride," he says. "It's the only ready-to-use antibiotic that doesn't require cows to be separated and milk to be discarded. It also has a short 3-day slaughter withdrawal, which helps producers keep their management options open."

More importantly, Dr. Chapman says clients who have used Cefenil RTU have been very happy with the results and the cost of the product. "It's very easy to administer—one subcutaneous or IM injection every day for five days—it's fast-acting, and very economical compared to other options. It is the right product at the right time for helping dairy producers under these current economic conditions."

For Dr. Chapman, managing metritis in dairy cows is about monitoring and expeditious treating with the right cost-effective tool. "A cow's attitude and appetite are key indicators to most health problems in the dairy, and three to 10 days in milk is the most important time to be monitoring," he says. "If metritis is diagnosed, treating it early with veterinarian-prescribed Cefenil RTU has shown to be a highly effective and economical way to get cows healthy and keep them producing."

REFERENCE
1. Overton M, Fetrow J. Economics of postpartum uterine health. In: Proceedings of the 2008 Dairy Cattle Reproduction Council Convention. 2008:39-44.

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Observe label directions and withdrawal times. Not for use in calves to be processed for veal. As with all drugs, the use of Cefenil® RTU (ceftiofur hydrochloride sterile suspension) is contraindicated in animals previously found to be hypersensitive to the drug. See product labeling for full product information.

616-26-122

Cefenil® RTU

(ceftiofur hydrochloride sterile suspension)

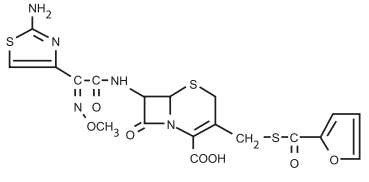
For intramuscular and subcutaneous use in cattle and intramuscular use in swine. This product may be used in lactating dairy cattle. Not for use in calves to be processed for veal.

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

CEFENIL® RTU (ceftiofur hydrochloride 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, 5.73 mg aluminum monostearate, 1.03 mg sorbitan monooleate and medium chain triglycerides.

Structure:



• HCl

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]amio]-3-[[(2-furanylcarbonyl) thio]methyl]-8-oxo-, hydrochloride salt [6R-[6α,7β(Z)]]-

INDICATIONS

Swine: CEFENIL RTU 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*.

Cattle: CEFENIL RTU 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 for 90 seconds to ensure complete resuspension 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 interval). 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.

CONTRAINDICATIONS

As with all drugs, the use of CEFENIL RTU 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 report suspected adverse drug events, for technical assistance or to obtain a copy of the safety data sheet (SDS), contact Norbrook at 1-866-591-5777. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

RESIDUE WARNINGS:

Swine: When used according to label indications, dosage, and route of administration, 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 of administration may result in illegal residues in edible tissues.

Cattle: When used according to label indications, dosage and route of administration, treated cattle must not be slaughtered for 3 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 and swine reproductive performance, pregnancy, and lactation have not been determined.

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.

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 or ceftiofur sodium sterile solution 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 ceftiofur hydrochloride sterile suspension, 50 mg/mL, or 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:	26.1 ± 5.02	29.2 ± 5.01
t_{max} h:	0.66 – 2.0 (range)	0.33 – 2.0 (range)
$AUC_{0\text{-}LOQ}$ 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 ± 0.791
$C_{72\ h}$ µg/mL:	0.518 ± 0.126	0.407 ± 0.0675
$t_{>0.2}$ 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 Cmax occurs, measured in hours.

$AUC_{0\text{-}LOQ}$ -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.

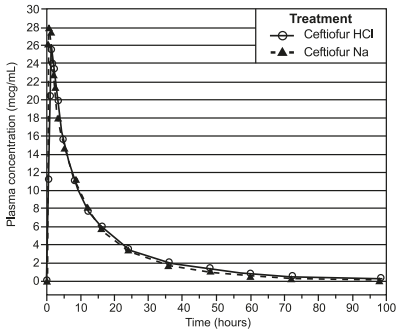
$C_{24\ h}$ - the concentration of drug at 24 h after administration.

$C_{72\ h}$ - 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.

Figure 2. Swine plasma concentrations of ceftiofur and desfuroylceftiofur metabolites after ceftiofur hydrochloride sterile suspension, 50 mg/mL, or 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 *Histophilus somni* 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 or ceftiofur sodium sterile solution 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.

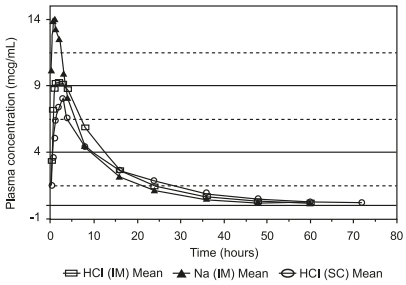
Table 2. Cattle plasma concentrations and related parameters of ceftiofur and desfuroylceftiofur metabolites after ceftiofur hydrochloride sterile suspension, 50 mg/mL, administered intramuscularly or subcutaneously at 1.0 mg ceftiofur equivalents /lb (2.2 mg/kg) BW and ceftiofur sodium sterile powder, 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
$AUC_{0\text{-}LOQ}$ µg·h/mL	160 ± 30.7	95.4 ± 17.8	115–142
$t_{1/2}$ h	12.0 ± 2.63	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. $AUC_{0\text{-}LOQ}$ -the area under the plasma drug concentrations 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 ceftiofur hydrochloride sterile suspension, 50 mg/mL, was administered either intramuscularly or subcutaneously or ceftiofur sodium sterile powder, 50 mg/mL, was administered intramuscularly at 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW.



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

CEFENIL RTU 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 bacteriocidal, *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*, 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 *Histophilus somni*, 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 Clinical and Laboratory Standards Institute (CLSI) Guidelines.

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
	Histophilus somni	109	1988 -1992	0.06	≤0.03-0.13
	Histophilus somni	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

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	189	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
	Histophilus somni	48	1997-1998	≤0.03	≤0.03-0.25
	Histophilus somni	87	1998-1999	≤0.03	≤0.03-0.125
	Histophilus somni	77	1999-2000	≤0.03	≤0.03-0.06
	Histophilus somni	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 CLSI.

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[1] 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.

Table 5. Acceptable quality control ranges for ceftiofur against Clinical and Laboratory Standards Institute 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***
Histophilus somni (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 (111 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 euthanized were necropsied and the lung lesions scored. On Day 15, all surviving animals were euthanized 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 ($P < 0.0001$). Rectal temperatures 24 h after third treatment were 104.0°F, 103.1°F and 102.8°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 ($P<0.05$) reduced Day 4 rectal temperature 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 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 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, 3, 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 (local 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.

TISSUE RESIDUE DEPLETION

Swine: 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.
Cattle: Two pivotal tissue residue decline studies were conducted in cattle. In the first study, cattle received an intramuscular injection of 1.0 mg of ceftiofur per lb body weight (2.2 mg of ceftiofur per kg body weight) for five consecutive days. Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in tissues such as kidney, liver and muscle by 3 days after dosing. In the second study, cattle received a subcutaneous injection of 1.0 mg of ceftiofur per lb body weight (2.2 mg of ceftiofur per kg body weight) for five consecutive days. Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in tissues such as kidney, liver and muscle by 3 days after dosing. These data collectively support a 3-day pre-slaughter withdrawal period in cattle when used according to label directions. In addition, two blood-level bioequivalence studies were conducted in cattle (one using subcutaneous administration and one using intramuscular administration). Blood concentrations of ceftiofur (measured as ceftiofur free acid equivalents) were greater than the analytical method's limit of quantification through 12 hours after administration, and these data demonstrated bioequivalence between Cefenil® RTU and the referenced listed new animal drug. These data support a zero-day milk discard time in lactating dairy cows.

STORAGE CONDITIONS

Do not store above 30ºC (86ºF). Shake well before using. Protect from freezing. Contents should be used within 42 days after the first dose is removed.

HOW SUPPLIED

CEFENIL RTU is available in 100 mL and 250 mL vials.

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

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