RESEARCH SUPPORTS SPECTRAMAST LC TREATMENT OF GRAM-NEGATIVE MASTITIS.

A NEW WAY OF THINKING

Groundbreaking new research published in the *Journal of Dairy Science*[1] is changing thinking about treatment for Gram-negative mastitis.

Research shows an 89% cure rate of mild or moderate Gram-negative mastitis caused by *Escherichia coli (E. coli)* — in which the cow is not sick or off feed but there are visible signs of mastitis — when using a five-day treatment with SPECTRAMAST® LC *(ceftiofur hydrochloride)* Sterile Suspension.

89%
CURE RATE

SIGNIFICANT RESPONSE TO TREATMENT

The Cornell University trial, conducted on five large commercial dairy herds in New York, investigated mild and moderate cases of Gram-negative mastitis and evaluated extended duration of therapy.

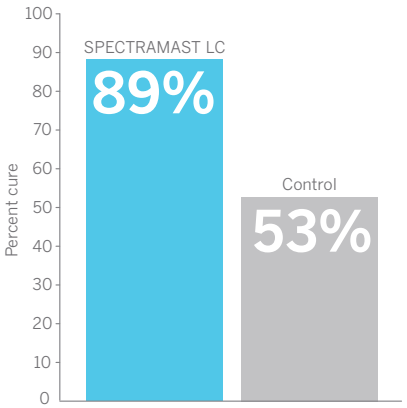
- For clinical mastitis caused by *E. coli*, 89% of the cows treated with SPECTRAMAST LC showed bacteriological — or complete — cures, compared with 53% of untreated control cows.
- Cows with a complete cure gave 8.8 more pounds of milk at the second test day when compared with cows that were not cured.*

8.8 MORE POUNDS OF MILK

- Herd survival was significantly higher in completely cured cows vs. noncured cows.

*(*P*<0.05)

COMPLETE CURE RATES FOR TREATMENT VS. CONTROLS OF *E. COLI*



Rate of complete cure between cows treated with SPECTRAMAST LC and nontreated controls for clinical mastitis caused by *E. coli*

FOR MORE INFORMATION, VISIT SPECTRAMAST.COM OR CONTACT YOUR ZOETIS REPRESENTATIVE.

Important Safety Information: Inappropriate dosage or treatment intervals for SPECTRAMAST LC or failure to adhere to proper milk discard period will result in violative milk residues. SPECTRAMAST LC requires a 72-hour milk discard period and a two-day pre-slaughter withdrawal period following the last treatment. SPECTRAMAST LC should not be used in animals found to be hypersensitive to the product.

SPECTRAMAST® LC (ceftiofur hydrochloride) Sterile Suspension

[1] Schukken YH, Bennett GJ, Zurakowski MJ, et al. Randomized Clinical Trial to Evaluate the Efficacy of a 5-day Ceftiofur Hydrochloride Intramammary Treatment on Nonsevere Gram-negative Clinical Mastitis. *J Dairy Sci* 2011;94(12):6203-6215.

SPECTRAMAST® LC

brand of ceftiofur hydrochloride sterile suspension

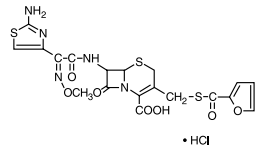
For **Intramammary** Infusion in Lactating Cows Only

FOR USE IN ANIMALS ONLY — NOT FOR HUMAN USE

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

DESCRIPTION: Ceftiofur hydrochloride is a cephalosporin antibiotic.

Chemical Structure of Ceftiofur Hydrochloride



U-64279A

• HCl

Chemical Name of Ceftiofur Hydrochloride

5-Thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid, 7 - [[2-(2 amino-4-thiazolyl) - 2 -(methoxyimino)acetyl]amino] - 3 - [[(2-furanylcarbonyl)thio] methyl] - 8 - oxo, hydrochloride.

SPECTRAMAST® LC Sterile Suspension is an oil based sterile suspension. Each 10 mL PLASTET® Disposable Syringe Contains:

Ceftiofur Equivalents (as the hydrochloride salt)	125 mg
Microcrystalline Wax	700 mg
Labrafil M 1944 CS	500 mg
Cottonseed Oil	q.s.

INDICATIONS FOR USE

SPECTRAMAST® LC (ceftiofur hydrochloride) Sterile Suspension is indicated for the treatment of clinical mastitis in lactating dairy cattle associated with coagulase-negative staphylococci, *Streptococcus dysgalactiae,* and *Escherichia coli*. Cows with systemic clinical signs caused by mastitis should receive other appropriate therapy under the direction of a licensed veterinarian.

DOSAGE

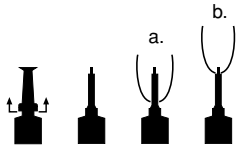
Infuse one (1) syringe into each affected quarter. Repeat this treatment in 24 hours. For extended duration therapy, once daily treatment may be repeated for up to 8 consecutive days.

DIRECTIONS FOR USING THE PLASTET DISPOSABLE SYRINGE

The syringe is designed to provide the choice of either insertion of the full cannula as has traditionally been practiced, or insertion of no more than 1/8 inch of the cannula, as reported by Eberhart RJ et al. 1987. Current Concepts of Bovine Mastitis, 3rd Edition, National Mastitis Council, Arlington, VA.

a. Full insertion: Remove the red end cap by pulling straight up as shown. Gently insert the full cannula into the teat canal; carefully infuse the product.

b. Partial insertion: Remove the red end cap by pulling straight up as shown. Gently insert the exposed white tip into the teat canal; carefully infuse the product.



ADMINISTRATION

Treatment: Wash teats thoroughly with warm water containing a suitable dairy antiseptic. Dry teats thoroughly. Milk out udder completely. Using an alcohol pad provided, wipe off the end of the affected teat using a separate pad for each teat. Choose the desired insertion length (full or partial) and insert tip into teat canal; push plunger to dispense entire contents, massage the quarter to distribute the suspension into the milk cistern.

Reinfection: After successful treatment, reinfection may occur unless good herd management, sanitation, and mechanical safety measures are practiced. Affected cows should be watched carefully to detect recurrence of infection and possible spread to other animals.

CONTRAINDICATIONS

As with all drugs, the use of **SPECTRAMAST® LC** Sterile Suspension is contraindicated in animals previously found to be hypersensitive to the drug.

Discard Empty Container: DO NOT REUSE
KEEP OUT OF REACH OF CHILDREN

WARNINGS

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. Sensitization of the skin may be avoided by wearing latex gloves.

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 report adverse effects in users, to obtain more information or to obtain a material safety data sheet, call 1-800-366-5288.

RESIDUE WARNINGS

1. Milk taken from cows during treatment (a maximum of eight daily infusions) and for 72 hours after the last treatment must not be used for human consumption.
2. Following label use for up to eight consecutive days, a 2-day pre-slaughter withdrawal period is required.
3. Use of this product in a manner other than indicated under DOSAGE might result in violative residues.

PRECAUTION

Following intramammary infusion with antibiotics in lactating cows, milk obtained during treatment and during the milk discard period should be properly discarded and not fed to calves.

CLINICAL MICROBIOLOGY

Ceftiofur is a broad-spectrum cephalosporin antibiotic that exerts its effect by inhibiting bacterial cell wall synthesis. Like other ß-lactam antimicrobial agents, the cephalosporins inhibit cell wall synthesis by interfering with the enzymes essential for peptidoglycan synthesis. This effect results in lysis of the bacterial cell and accounts for the bactericidal nature of these agents. Ceftiofur has demonstrated *in vitro* activity against clinical isolates and isolates from diagnostic laboratories. The results of susceptibility testing of organisms are presented in Table 1 and Table 2.

Table 1. Ceftiofur Minimum Inhibitory Concentrations (MIC) Values of Isolates from Field Studies Evaluating Clinical Mastitis in Dairy Cows in the U.S. During 2000

Pathogen	Number of Isolates	MIC_{90}* (µg/mL)	MIC range (µg/mL)
Coagulase-negative staphylococci (CNS)	33	1.0	≤0.06–2.0
Streptococcus dysgalactiae	32	≤0.06	≤0.06–0.05
Escherichia coli	35	0.5	≤0.06–1.0

*MIC for 90% of the isolates.

Table 2. Ceftiofur MIC values* for mastitis pathogens from diagnostic laboratories in the U.S. and Canada

Organism	No.	Date isolated	MIC_{90}** (µg/mL)	MIC range (µg/mL)
Staphylococcus aureus	135	1991–1992	1.0	0.13 to 2.0
	10	1993	1.0	0.25 to 1.0
	107	1995	1.0	0.25 to 2.0
	61	2000	1.0	≤0.06 to 2.0
Coagulase (-) staphylococci	139	2000–2001	1.0	≤0.06 to 2.0
Streptococcus dysgalactiae	15	1991–1992	1.0	≤0.06 to 2.0
	15	1993	≤0.0039	No range†
	152	1997–1999	0.25	0.25 to 4.0
	64	2000	≤0.06	≤0.06 to 0.5
Streptococcus uberis	22	1991–1992	0.5	≤0.06 to 4.0
	15	1993	0.03	≤0.0039 to 0.06
	133	1997–1999	0.5	0.5 to 8.0
	20	2000	1.0	≤0.06 to 2.0
Escherichia coli	39	1991–1992	1.0	0.25 to 1.0
	40	1993	0.5	0.13 to 1.0
	52	2000	0.5	≤0.06 to 1.0

*The above *in vitro* data are available, but their clinical significance is unknown.

**The MIC for 90% of the isolates.

†No range, all isolates yielded the same value.

Based on pharmacokinetic, milk residue and clinical effectiveness studies in dairy cattle following intramammary infusion of ceftiofur and the MIC and disk (30 µg) diffusion data from mastitis pathogens, the following breakpoints are recommended by the Clinical and Laboratories Standards Institute (CLSI) (Table 3).

Table 3. Current recommended interpretive criteria established by CLSI for ceftiofur for Bovine Mastitis

Bovine Mastitis Organisms	Disk Content	Zone diameter (mm)			MIC breakpoint (µg/mL)		
		S	I	R	S	I	R
Staphylococcus aureus	30 µg	≥21	18–20	≤17	≤2.0	4.0	≥8.0
Streptococcus dysgalactiae							
Streptococcus uberis							
Streptococcus agalactiae							
Escherichia coli							

S – Susceptible I – Intermediate R – Resistant

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 ceftiofur hydrochloride (Table 4).

Table 4. Acceptable Quality Control Ranges for Ceftiofur Against CLSI Recommended American Type Culture Collection (ATCC) Reference Strains

Organism Name (ATCC No.)	Zone diameter (mm) (Disk Content 30 µg/mL)	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

EFFECTIVENESS

In 1999 to 2000, the efficacy of ceftiofur was demonstrated in a pivotal multi-location field trial in lactating dairy cattle with clinical mastitis in one quarter. Ceftiofur was formulated in stable cottonseed oil sterile suspension manufactured under GMP guidelines. Cows with mastitis were enrolled in the study if visually abnormal milk (clots, flakes, or watery secretion) or if udder swelling, heat, pain or redness were present and the milk was not yet visually abnormal but California Mastitis Test (CMT) gave results of 2 or greater. A total of 13 trial sites enrolled 352 cows in the study. Cows were assigned to one of three treatment groups: non-treated control, 62.5 mg ceftiofur, and 125 mg ceftiofur. Each treatment group received an intramammary infusion twice at a 24-hour interval in the affected quarter. The non-treated controls received no therapy. Three different definitions for cure were used for analysis purposes: 1) a clinical cure was defined as the milk and udder returning to normal 14 days after the last treatment and remaining normal at the 21-day time point; 2) a bacterial cure was defined as the absence of the pre-treatment pathogen at 14 and 21 days post-treatment; 3) a protocol cure was defined as the absence of the pre-treatment pathogen at 14 and 21 days post-treatment and return to normal of the milk and udder 14 days after the last treatment and remaining normal at the 21 day time point. Three hundred and thirty-seven cows were analyzed for clinical cure rates, which were 54.7% (64/117) for the non-treated control group compared to 69.4% (75/108) for the 62.5 mg treatment group and 78.6% (88/112) for the 125 mg treatment group. The 125 mg treatment group's clinical cure rate was significantly greater than the non-treated control ($P = 0.002$). One hundred and forty-six cows were analyzed for bacterial cure rates, which were 41.3% (19/46) for the non-treated control group, 45.6% (21/46) for the 62.5 mg treatment group and 70.4% (38/54) for the 125 mg treatment group. The 125 mg treatment group's bacterial cure rate was significantly greater than the non-treated control group ($P = 0.006$). One hundred and forty-six cows were analyzed for protocol cure rates, which were 63.0% (34/54) for the 125 mg treatment group, 41.3% (19/46) for the 62.5 mg treatment group and 23.9% (11/46) for the non-treated control group. The 125 mg treatment group's protocol cure rate was significantly better than the non-treated control ($P < 0.001$) for treatment of clinical mastitis. Thus, 125 mg of ceftiofur administered via intramammary infusion twice at a 24-hour interval was effective in the treatment of clinical mastitis in lactating dairy cows associated with coagulase-negative staphylococci, (CNS), *Streptococcus dysgalactiae*, and *Escherichia coli*.

ANIMAL SAFETY

A pivotal GLP udder irritation study was conducted in 40 cows to assess udder irritation following daily intramammary infusion of an oil-based suspension containing 125 mg of ceftiofur for up to 8 consecutive days. A transient and clinically insignificant rise in SCC to levels <200,000 cell/mL was observed following infusion in normal cows with very low pre-infusion SCC (<10,000 cell/mL). This elevation is not unexpected with oil-based suspensions. The duration of therapy did not affect this elevation. No udder clinical signs of irritation (swelling, pain, or redness), changes in body temperature or in milk production were noted during this study. This pivotal GLP study demonstrated that this formulation is clinically safe and non-irritating to the udder of lactating dairy cows. In two clinical field efficacy studies in 971 lactating dairy cows, no reports of udder irritation or adverse events were noted following infusion. Collectively, these three studies demonstrate that the intramammary infusion of an oil-based suspension containing 125 mg of ceftiofur once daily into all four quarters for up to 8 consecutive days is clinically safe and non-irritating to the udder of lactating dairy cows.

MILK AND TISSUE RESIDUE DEPLETION

A metabolism study in cattle using radiolabeled ceftiofur provided the data to establish tolerances for ceftiofur-related residues (as desfuroylceftiofur) in tissue and milk. These tolerances are 0.1 ppm in milk, 0.4 ppm in kidney, 2.0 ppm in liver and 1.0 ppm in muscle.

Two pivotal milk residue decline studies were conducted. In these studies, nonmastitic cows received 125 mg of ceftiofur per quarter into all four quarters either twice at a 24-hour interval or once daily for 8 consecutive days. Regardless of treatment duration and using a tolerance of 0.10 ppm for ceftiofur-related residues in milk, these studies demonstrate that milk taken during treatment (a maximum of 8 consecutive daily infusions) and for 72 hours after the last treatment must not be used for human consumption and must be discarded.

A pivotal tissue residue decline study in lactating dairy cattle provides tissue residue decline data. In this study, the cattle received an intramammary infusion of 125 mg of ceftiofur hydrochloride into each of four quarters once daily for 8 consecutive days. Ceftiofur residues were determined in the kidney (the target tissue) using the official analytical method. Kidney residues were less than the established tolerance (0.4 ppm) by 2 days after the last infusion. These data collectively support the assignment of a 2-day pre-slaughter withdrawal period regardless of treatment duration.

STORAGE CONDITIONS

Store at Controlled Room Temperature 20° to 25° C (68° to 77° F) [See USP]. Protect from light. Store plastets in carton until used.

HOW SUPPLIED

SPECTRAMAST® LC Sterile Suspension is available in cartons containing one (1) unbroken package of 12–10 mL PLASTET® Disposable Syringes with 12 individually wrapped 70% isopropyl alcohol pads and in pails containing 12 unbroken packages of 12-10 mL PLASTET® Disposable Syringes with 144 individually wrapped 70% isopropyl alcohol pads.

NADA# 141-238, Approved by FDA

Distributed by:
Pfizer Animal Health
Division of Pfizer Inc, NY, NY 10017

www.spectramast.com or call 1-800-733-5500

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