

JUN 2 2006

Date of Approval:

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-238

SPECTRAMAST LC Sterile Suspension
(ceftiofur hydrochloride)

To establish a 2-day pre-slaughter withdrawal period for cattle

Sponsored by:
Pharmacia & Upjohn Co.,
a Division of Pfizer, Inc.

2006-141-238

FOIS 2

1. GENERAL INFORMATION:

- a. File Number: NADA 141-238
- b. Sponsor: Pharmacia & Upjohn Co.
a Division of Pfizer, Inc.
235 East 42d St.
New York, NY 10017
Drug Labeler Code: 000009
- c. Established Name: Ceftiofur hydrochloride
- d. Proprietary Name: SPECTRAMAST LC Sterile Suspension
- e. Dosage Form: Sterile oil suspension
- f. How Supplied: 10 mL plastic syringes (PLASTETS) with cannula
- g. How Dispensed: Rx
- h. Amount of Active Ingredient: Each PLASTET contains ceftiofur hydrochloride equivalent to 125.0 mg ceftiofur (12.5 mg/mL).
- i. Route of Administration: Intramammary infusion
- j. Species/Class: Bovine/lactating dairy cattle
- k. Recommended 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.
- l. Pharmacological Category: Antimicrobial
- m. Indications: SPECTRAMAST LC Sterile Suspension (ceftiofur hydrochloride) 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.
- n. Effect of Supplement: To establish a 2-day pre-slaughter withdrawal period for cattle

2. EFFECTIVENESS:

CVM did not require effectiveness studies for this supplemental approval. The FOI Summary for the original approval of SPECTRAMAST LC Sterile Suspension (NADA 141-238) dated February 9, 2005, contains a summary of studies that demonstrate effectiveness of the drug for cattle.

3. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of SPECTRAMAST LC Sterile Suspension (NADA 141-238) dated February 9, 2005, contains a summary of target animal safety studies for cattle.

4. HUMAN FOOD SAFETY:**A. Toxicology**

The toxicity testing of ceftiofur is summarized in the FOI Summary for the original approval of NAXCEL Sterile Powder (NADA 140-338) dated January 25, 1988, and in the FOI Summary dated April 1996, for the original approval of EXCENEL RTU (ceftiofur hydrochloride) Sterile Suspension (NADA 140-890) for use in swine. Tolerances for cattle are summarized in the FOI Summary for EXCEDE Sterile Suspension (NADA 141-209, approved September 5, 2003).

Safe concentrations are established for cattle as follows:

Muscle:	4.4 ppm
Liver:	13.2 ppm
Kidney:	26.4 ppm
Fat:	26.4 ppm
Injection site:	166 ppm
Milk:	0.320 ppm

B. Residue Chemistry

The total residue depletion and metabolism in the target species and comparative metabolism in the toxicological species for ceftiofur are summarized in the FOI Summaries under NADA 140-338 and NADA 140-890. The following pivotal study was conducted to confirm applicable withdrawal periods in cattle.

1. Study

“Concentration of Ceftiofur Residues in Tissues of Lactating Dairy Cows at Various Intervals Following the IMM Administration of 125 mg Ceftiofur HCl

(PNU-64279A) per Quarter per Day into All 4 Quarters of the Udder for 8 Consecutive Days.” Study Number: 2000-0431.

Principal Investigators: R.E. Hornish and M.J. Prough, Pfizer Animal Health, Kalamazoo, MI

Animal Species: Bovine

Breed: Holstein

Number of Animals/Sex: 25, all lactating female

Weights of Animals: 582-819 kg

Parity: 1st through 4th lactation

Health Status: Clinically healthy

Average Pre-Dose Milk Production: 32.3 ± 4.2 kg

Route of Administration: intramammary (IMM)

Dose Rate: 125 mg CE/quarter into all 4 quarters/day (total daily dose = 500 mg)

Duration of Dosing: one infusion into each quarter daily for eight consecutive days

Marker Residue Depletion Data: Samples of kidney, liver, muscle, and fat were assayed for desfuroylceftiofur-related residue by the HPLC-DCA assay. The results of the assays are provided in Table 1 below. The limit of quantification (LOQ) of the assay was 0.10 ppm, and the limit of detection (LOD) was 0.030 ppm.

Table 1. Mean Concentration of Cefitofur and Desfuroylceftiofur-related Residue (as DCA) in the Tissues of Lactating Dairy Cattle Following the Daily Intramammary Administration of 125 mg of Cefitofur Hydrochloride Into All Four Quarters for Eight Consecutive Days

Slaughter Group	Mean Concentration of Cefitofur Residue as DCA, ppm			
	Kidney	Liver	Muscle	Fat
12-hour Withdrawal	0.277 ± 0.049	<LOQ	< LOD	< LOD
24-hour Withdrawal	0.172 ± 0.056	<LOQ	< LOD	< LOD
36-hour Withdrawal	0.112 ± 0.001	<LOQ	< LOD	< LOD
48-hour Withdrawal	<LOQ	< LOD	< LOD	< LOD
72-hour Withdrawal	< LOD	< LOD	< LOD	< LOD

At all time points, kidney is the tissue with the highest relative residue concentration.

2. Target Tissue and Marker Residue

The target tissue for residue monitoring is kidney. The marker residue in edible tissues, including milk, is the sum of ceftiofur and desfuroylceftiofur-related metabolites, measured by HPLC as the stable derivative desfuroylceftiofur acetamide (DCA).

3. Tolerances

Cattle tolerances are: 0.4 ppm DCA in kidney, 2 ppm DCA in liver, 1 ppm DCA in muscle, and 0.1 ppm DCA in milk. For research purposes, a value of 95 ppm DCA has been established for making decisions regarding the safety of the injection site.

4. Withdrawal Period

The residue data of this study were analyzed by a statistical method which determines the statistical tolerance limit for the 99th percentile of the population with a 95% confidence as outlined in the FDA's *Guideline for Establishing a Withdrawal Period*. The tolerance limit falls below the kidney tolerance of 0.4 ppm at 25 hours after the last dose. The data support the assignment of a 48-hour (2-day) pre-slaughter withdrawal period for the IMM administration of SPECTRAMAST LC Sterile Suspension in lactating dairy cattle when used according to label directions.

5. Milk Discard

The milk tolerance has not changed. Consequently, no milk out data were required and the 72-hour discard can be maintained.

C. Microbial Food Safety

FDA concluded the impact of the proposed supplemental application on microbial food safety was not of a magnitude that required a hazard characterization or a full microbial food safety assessment.

D. Analytical Methods for Residues

The regulatory method for determination of DCA in bovine kidney, muscle, and milk is the HPLC-DCA assay which successfully completed a sponsor-monitored multi-laboratory method trial. The method is on file with the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

5. **USER SAFETY:**

Studies to evaluate the safety of ceftiofur to users are discussed in detail in the original FOI Summary for NAXCEL Sterile Powder (NADA 140-338) dated January 25, 1988.

Human Warnings are provided on the product labeling as follows:

Discard empty container: Do not reuse. 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. 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.

6. **AGENCY CONCLUSIONS:**

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that SPECTRAMAST LC Sterile Suspension, when administered according to the label directions, is safe and effective for the treatment of clinical mastitis in lactating dairy cattle associated with coagulase-negative staphylococci, *Streptococcus dysgalactiae*, and *Escherichia coli*.

Labeling restricts this drug to use by or on the order of a licensed veterinarian. This decision was based on the following factors: (a) adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this product to treat clinical mastitis, and (b) restricting this drug to use by or on the order of a licensed veterinarian should help prevent indiscriminate use which could result in violative tissue residues.

In accordance with 21 CFR 514.106(b)(2) this is a Category II change which did not require a reevaluation of safety and effectiveness data in the parent application.

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

No patent information was submitted with this application.

7. ATTACHMENTS:

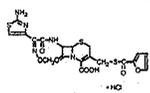
Facsimile labeling is attached as indicated below.

- A. SPECTRAMAST LC Sterile Suspension - PLASTET Label
- B. SPECTRAMAST LC Sterile Suspension – Carton Label
- C. SPECTRAMAST LC Sterile Suspension - Package Insert

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 (FDA) 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



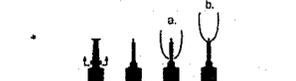
U-54273A
Chemical Name of Ceftiofur Hydrochloride
5-[7-[[4-azabicyclo[2.2.1]hept-2-ylideneamino]heptan-2-ylideneamino]-7-oxo-7-oxa-1-azabicyclo[2.2.1]heptan-2-ylideneamino]-2-oxo-1,4-dihydro-6,6-dimethyl-5H-thiazolo[5,4-d]thiazine-5-carboxylic acid hydrochloride
SPECTRAMAST® LC Sterile Suspension is an off-white sterile suspension.
Each 10 mL PLASTETM Disposable Syringe Contains:
Ceftiofur Hydrochloride (as the hydrochloride salt) 125 mg
Microcrystalline Wax 700 mg
Lactanil M 1544 CE 300 mg
Cottonseed Oil 0.5

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



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

DIRECTIONS FOR USING THE PLASTETM DISPOSABLE SYRINGE
The syringe is designed to protect the sterility of the milk canula as it has traditionally been practiced, or insertion of no more than 1/8 inch of the canula, as reported by Chang, R. J., et al. 1993. Current Concepts of Bovine Mastitis, 3rd Edition, National Mastitis Council, Arlington, VA.
a. Full Insertion: Remove the red cap and cap by pulling straight up as shown. Gently insert the red cap into the red canula. Carefully insert the product.
b. Partial Insertion: Remove the red cap and cap by pulling straight up as shown. Gently insert the red cap only so no red canula canula into the product.



ADMINISTRATION
Treatment: Wash thoroughly with warm water containing a suitable dairy antiseptic. Dry teat 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 (1/8 or partial) and insert to into teat canal. Push plunger to dispense entire contents. Maintain the quarter in milk until the milk clots.
Reinsertion: After successful treatment, reinsertion may occur unless good herd management, sanitation, and mechanical milking measures are practiced. Affected cows should be rechecked carefully to detect recurrence of infection and 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.

Warnings
Females and cephalosporins can cause allergic reactions in sensitized individuals. Special cautions as such, including cephalosporins, may exist mild to severe allergic reactions. Hypersensitivity reactions may lead to anaphylaxis. Avoid direct contact of the product with the skin, eyes, mouth and clothing. Sensitization of the animal may be prevented by washing the drug.
Persons with a known hypersensitivity to penicillins or cephalosporins should avoid exposure to this product.
In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental injection, wash with water. Remove contaminated clothing. If allergic reaction occurs (e.g., skin rash, hives, difficulty breathing), seek medical attention. This material contains more detailed contraindications, safety information, to report adverse effects or usage. To obtain more information or to obtain a material safety data sheet, call 1-800-355-5558.

RESIDUE WARNINGS
1. Milk from cows during treatment (a maximum of eight daily injections) 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 7-day pre-residue withdrawal period is required.
3. Use of this product in a manner other than indicated under DOSEAGE might result in residue residues.

PRECAUTIONS
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 synthesis. Like other drugs that are antimicrobials, the cephalosporins should not be used in conjunction with the enzymes essential for penicillin synthesis. This effect results in high levels of the drug and activity for the cephalosporins and other 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 ^a (µg/mL)	MIC Range (µg/mL)
<i>Corynebacterium</i>	30	1.0	0.06-2.0
<i>Staphylococcus aureus</i> (MSSA)	32	0.5	0.06-0.5
<i>Staphylococcus dysgalactiae</i>	32	0.5	0.06-1.0
<i>Escherichia coli</i>	32	0.5	0.06-1.0

^a 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. Isolates	Date	MIC ^a (µg/mL)	MIC range (µg/mL)
<i>Staphylococcus aureus</i>	125	1991-1992	1.0	0.15 to 2.0
	10	1993	1.0	0.25 to 1.0
	102	1996	1.0	0.43 to 2.0
	61	2000	1.0	0.06 to 2.0
<i>Corynebacterium</i>	136	2000-2001	1.0	0.06 to 2.0
	15	1991-1992	1.0	0.06 to 2.0
	15	1993	0.0039	No range
<i>Streptococcus dysgalactiae</i>	152	1991-1999	0.5	0.06 to 4.0
	24	2000	0.06	0.06 to 0.5
	22	1991-1992	0.5	0.06 to 4.0
	15	1993	0.5	0.0025 to 0.6
<i>Streptococcus uberis</i>	133	1993-1999	0.5	0.5 to 8.0
	20	2000	1.0	0.06 to 2.0
	38	1991-1992	1.0	0.15 to 1.0
<i>Escherichia coli</i>	49	1993	0.5	0.12 to 1.0
	82	2000	0.5	0.06 to 1.0

^a The above in vitro data are available, but their clinical significance is unknown.
^b The MIC for 90% of the isolates.
^c No range, as isolates yielded the same value.

SPECTRAMAST® LC
brand of ceftiofur hydrochloride sterile suspension

Based on pharmacokinetic, milk residue and clinical effectiveness studies in dairy cattle showing intramammary infusion of ceftiofur and the MIC and zone diameter data from mastitis pathogens, the following breakpoints are recommended by the National Committee for Clinical Laboratory Standards (now the Clinical and Laboratory 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
<i>Staphylococcus aureus</i> <i>Streptococcus dysgalactiae</i> <i>Streptococcus uberis</i> <i>Streptococcus saprophyticus</i> <i>Escherichia coli</i> E - Susceptible I - Intermediate R - Resistant	30 µg	≥21	16-20	≤17	≤0.4	4.0	≥8.0

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 strains (or disks) 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)
<i>Escherichia coli</i> (25922)	28-31	0.25-1.0
<i>Staphylococcus aureus</i> (29212)	27-31	0.25-1.0
<i>Streptococcus aureus</i> (29522)	27-31	0.25-1.0
<i>Fusidomonas axiphila</i> (77833)	14-18	156-64.0

EFFECTIVENESS
In 1995 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 sterile off-white sterile suspension manufactured under GMP guidelines. Cows with mastitis were enrolled in the study if visually abnormal with clots, flakes, or watery secretion of color, swelling, heat, pain or redness were present and the milk was not visually abnormal by California Mastitis Test (CMT) gave results of 2 or greater. A total of 13 trial areas enrolled 352 cows to 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 statistical purposes: 1) a clinical cure was defined as the milk and udder returned 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. These hundred and thirty seven cows were analyzed for bacterial cure rates, which were 64.7% (64/117) for the non-treated control group, 45.8% (41/144) for the 62.5 mg treatment group and 70.4% (63/90) for the 125 mg treatment group. The 125 mg treatment group had a bacterial cure rate was significantly greater than the non-treated control group (P=0.008). One hundred and thirty six cows were analyzed for protocol cure rates, which were 60.2% (64/106) for the 125 mg treatment group, 41.3% (15/44) for the 62.5 mg treatment group and 23.8% (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 as intramammary infusion twice at a 24-hour interval was effective in the treatment of clinical mastitis in lactating dairy cows associated with contagious negative streptococci, *C. S.*, *S. D.*, and *E. coli*.

ANIMAL SAFETY
A pivotal CLP udder infusion study was conducted in 40 cows to assess udder infusion following daily intramammary infusion of an off-white suspension containing 125 mg of ceftiofur for up to 8 consecutive days. A transient and clinically insignificant rise in SCC to levels <200,000 cells/mL was observed following infusion in normal cows with very low pre-infusion SCC (<150,000 cells/mL). This elevation is not unexpected with off-white suspensions. The duration of therapy did not affect the elevation. No other clinical signs of irritation (swelling, pain, or redness), changes in udder temperature or milk production were noted during this study. This pivotal CLP study demonstrated that the formulation is clinically safe and non-irritating to the udder of lactating dairy cows. In two other field efficacy studies in 771 lactating dairy cows, no reports of udder irritation or adverse events were noted following infusion. Collectively, these studies demonstrate that the intramammary infusion of an off-white suspension containing 125 mg of ceftiofur once daily into each quarter for up to 8 consecutive days is clinically safe and non-irritating to the udder of lactating dairy cows.

MILK AND TISSUE RESIDUE DELETION
A metabolism study in cattle using radiolabeled ceftiofur provided the data to establish withdrawal periods for ceftiofur in milk and tissues and milk. These withdrawal periods are 0.1 ppm in milk, 0.1 ppm in udder, 2.0 ppm in liver, and 1.0 ppm in muscle. Two studies in milk residue depletion in lactating dairy cows, not administered ceftiofur received 125 mg of ceftiofur per quarter into all four quarters twice at a 24-hour interval or once daily for the larger volume using the off-white suspension method. Only residues were less than the established tolerance of 0.1 ppm by 2 days after the last infusion. These data collectively support the establishment of a 2-day pre-residue 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 in plastic in carton used.

HOW SUPPLIED
SPECTRAMAST® LC Sterile Suspension is available in cartons containing 1 vial (10 mL) PLASTETM Disposable Syringe with 13 individually wrapped 30% isotonic alcohol pads.
H348A 1-01-026. Approved by FDA.

Distributed by
Pharmacia & Upjohn Company
Division of Pharm. Inc. NY, NY 10017
www.spectramast.com or call
1-800-733-5500
Revised: February 2006 018 774 000
02-01 4758-03-000

SPECTRAMAST® LC
brand of cefotiofur hydrochloride
sterile suspension

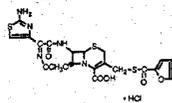
For Intramammary Infusion in Lactating Cows Only

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

Cefotiofur hydrochloride is a cephalosporin antibiotic.
Chemical Structure of Cefotiofur Hydrochloride



U-84279A
Chemical Name of Cefotiofur Hydrochloride
5-Thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid, 7-[(2R)-2-amino-4-thiazoly]-2-[(2R)-2-mercaptoethyl]amino-3-[[(2S)-2-mercaptoethyl]amino]-8-oxo-1,6-dioxo-1,2,3,4-tetrahydro-1,2,4-benzodiazepine-6-carboxylic acid hydrochloride.
SPECTRAMAST® LC Sterile Suspension is an oil based sterile suspension.
Each 10 mL PLASTET® Disposable Syringe Contains:
Cefotiofur Equivalents (as the hydrochloride salt) 125 mg
Microcrystalline Wax 700 mg
Labile M: 1046 GS 500 mg
Cottonseed Oil q.s.

INDICATIONS FOR USE
SPECTRAMAST® LC Sterile Suspension (cefotiofur hydrochloride) 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.



DOSEAGE
Inject 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 reinsertion 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, R.J., 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 daily 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 the teat canal; push plunger to dispense entire contents, massage the quarter to distribute the suspension into the milk cluster.
Reinsertion: After successful treatment, reinsertion 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 promptly 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. Toxic exposures to such antimicrobials, including cefotiofur, may elicit mild to severe allergic reactions in some individuals. Hypersensitivity or allergic reactions 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, difficulty breathing), seek medical attention.
The material safety data sheet contains more detailed occupational safety information. To obtain accurate information in Spanish, to obtain more information or to obtain a material safety data sheet call 1-800-366-2000.

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 DOSEAGE 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
Cefotiofur is a broad-spectrum cephalosporin antibiotic that exerts its effect by inhibiting bacterial cell wall synthesis. Like other beta-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. Cefotiofur 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. Cefotiofur 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 ^a (µg/mL)	MIC Range (µg/mL)
Coagulase-negative staphylococci (CNS)	33	1.0	50.06-2.0
Streptococcus dysgalactiae	32	20.06	50.06-0.5
Escherichia coli	35	0.5	50.06-1.0

^a MIC for 90% of the isolates

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

Organism	No.	Date Isolated	MIC ^a (µg/mL)	MIC Range (µg/mL)
Staphylococcus aureus	126	1991-1992	1.0	0.13 to 2.0
	10	1993	1.0	0.25 to 1.0
	87	1995	1.0	0.25 to 2.0
Coagulase (+) staphylococci	139	2000-2001	1.0	50.06 to 2.0
	15	1991-1992	1.0	50.06 to 2.0
	15	1993	50.0039	No range ^b
Streptococcus dysgalactiae	152	1997-1999	0.25	0.25 to 0.6
	64	2000	50.06	50.06 to 0.5
	22	1991-1992	0.5	50.05 to 4.0
Streptococcus uberis	15	1993	0.03	50.0039 to 0.06
	133	1997-1999	0.5	0.5 to 0.6
	32	2000	1.0	50.06 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	0.3	50.06 to 1.0

^a The above in vitro data are available, but their clinical significance is unknown.
^b The MIC for 10% of the isolates.
^c No range, all isolates yielded the same value.

SPECTRAMAST® LC
brand of cefotiofur hydrochloride sterile suspension

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

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

Bovine Mastitis Organisms	Disk Content	Zone Diameter (mm)			MIC breakpoint (µg/L)		
		S	I	R	S	I	R
Staphylococcus aureus	30 µg	≥21	16-20	≤17	≤2.0	4.0	≥8.0
Streptococcus dysgalactiae							
Streptococcus uberis							
Streptococcus agalactiae							
Escherichia coli							
S = Susceptible							
I = Intermediate							
R = Resistant							

Table 4. Acceptable Quality Control Ranges for Cefotiofur Agalact (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)	27-31	0.25-1.0
Staphylococcus aureus (28625)	27-31	0.25-1.0
Pseudomonas aeruginosa (27853)	14-18	160-64.0

Standardized procedures require the use of laboratory control organisms for both standardized diffusion techniques and standardized disk techniques. The 30 µg cefotiofur sodium disk should show the following zone diameters and the cefotiofur sodium standard reference powder (disk) should provide the following MIC values for the reference strain. Cefotiofur sodium disk or powder reference standards appropriate for cefotiofur hydrochloride (Table 4).

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EFFECTIVENESS
In 1996 to 2000, the efficacy of cefotiofur was demonstrated in a pivotal multi-location field trial in lactating dairy cattle with clinical mastitis in one quarter. Cefotiofur was formulated in stable compound of sterile suspension manufactured under GMP guidelines. Cows with mastitis were enrolled in the study if visually abnormal milk (pus, flakes, or watery secretion) or if udder swelling, heat, pain or redness were present and the milk was not yet visually abnormal by 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, 0.25 mg cefotiofur and 125 mg cefotiofur. Each treatment group received intramammary infusion under aseptic conditions at 24-hour intervals for the first 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 remaining normal at the 21 day time point. Three hundred and thirty seven cows were analyzed for clinical cure rates, which were 34.7% (64/171) for the non-treated control group, 66.4% (109/164) for the 0.25 mg treatment group and 78.6% (88/112) for the 125 mg treatment group. The 125 mg treatment group clinical cure rate was significantly greater than the non-treated control (P<0.0001). One hundred and forty six cows were analyzed for bacterial cure rates, which were 63.2% (54/86) for the 125 mg treatment group, 41.3% (16/46) for the 0.25 mg treatment group and 23.9% (11/46) for the non-treated control group. The 125 mg treatment group's post-treatment cure rate was significantly better than the non-treated control (P<0.0001) in treatment of clinical mastitis. Thus, 125 mg of cefotiofur administered via intramammary infusion twice at 24-hour intervals 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 GMP under infusion study was conducted in 40 cows to assess udder infection following daily intramammary infusion of an oil based suspension containing 125 mg of cefotiofur for up to 8 consecutive days. A transient and clinically insignificant rise in SCC to levels <200,000 cells/mL was observed following infusion in normal cows with very low pre-infusion SCC (<10,000 cells/mL). This elevation is not unexpected with oil-based suspensions. The duration of therapy did not affect this elevation. No other clinical signs of irritation (swelling, pain, or redness), changes in body temperature or in milk production were noted during this study. This pivotal GMP 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 cefotiofur once daily into 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 cefotiofur provided the data to establish tolerances for cefotiofur-related residues (as deacetylceftiofur) 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 parallel milk residue depletion studies were conducted. In these studies, non-mastitic cows received 125 mg of cefotiofur 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 cefotiofur-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.

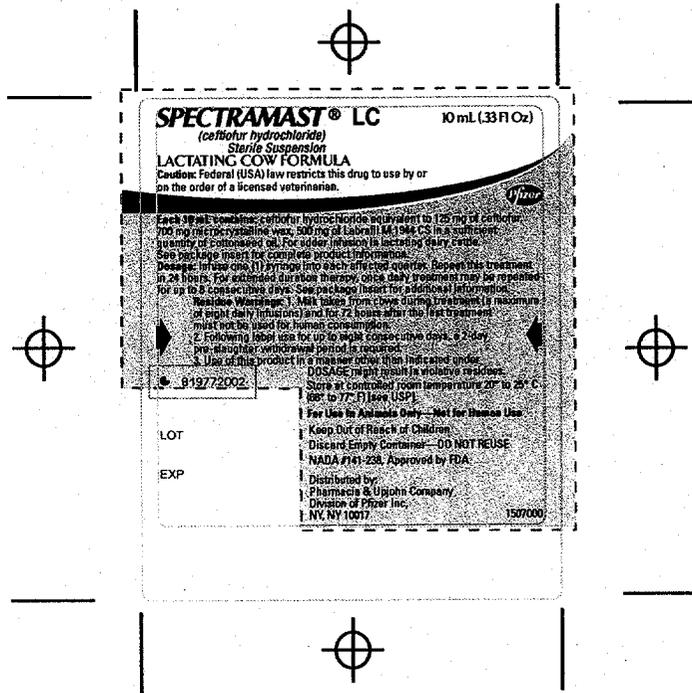
STORAGE CONDITIONS
Store at Controlled Room Temperature 20° to 25° C (68° to 77° F) (see USP). Protect from light. Store plasters in carton until used.

HOW SUPPLIED
SPECTRAMAST® LC Sterile Suspension is available in cartons containing 1 number 10-100 mL PLASTET® Disposable Syringe with 12 individually wrapped 70% isopropyl alcohol pads.
NADA# 141-238, Approved by FDA

Pharmacia & Upjohn Company
Division of Pfizer Inc, NY, NY 10017

www.spectramast.com or call 1-800-233-5500
819 774 003
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4788-33-000

Revised: February 2006



 PACKAGE DESIGN & DEVELOPMENT KALAMAZOO	Spectramast LC	23FEB06	819 772 002	2
	3583	USA		
	P. Hofpar R. Stafford L. Amos	2.738 x 2.25 inches	693416	PD1877 R5
	0009-5279-01	4758-33	.75 x .843 inches	label
Additional Info (PIC #): Varnish all except for the imprint area and overlap area	Colors:  Black  PMS 286  PMS 116  Dietline  Varnish			

For use in Animals Only
 For other Infusions in lactating dairy cattle.
 CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.
 PLASTET® Disposable Syringes
 Equivalent to 125 mg cefbutor per 10 ml
 NADA #141-238, Approved by FDA

LACTATING COW FORMULA

SPECTRAMAST® LC
 (ceftiofur hydrochloride)
 Sterile Suspension



773754

For use in Animals Only - Not for Human Use - Keep out of reach of children - Discard Empty Containers - DO NOT REUSE
 Store at controlled room temperature 20° to 25° C (68° to 77° F) (see USP). Protect from light. Store plastic in carton until used. See package insert for complete product information.

INDICATIONS
 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.

ADMINISTRATION
 Treat: Wash teats thoroughly with warm water containing a suitable daily antiseptic. Dry teats thoroughly. Milk out under complete relief. 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 system.

Relief: 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.

RESIDUE WARNINGS

- 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.
- Following label use for up to eight consecutive days, a 2-day pre-slaughter withdrawal period is required.
- Use of this product in a manner other than indicated under DOSAGE might result in violative residues.

DESCRIPTION
 Each 10 ml PLASTET® Disposable Syringe Contains:
 Cefbutor equivalent (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 Sterile Suspension (ceftiofur hydrochloride) 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.

READ RESIDUE WARNINGS

DISCARD MILK FOR 72 hrs AFTER LAST TREATMENT

DO NOT Slaughter COW FOR 2 days AFTER TREATMENT

SPECTRAMAST® LC
 (ceftiofur hydrochloride)
 Sterile Suspension
LACTATING COW FORMULA

Equivalent to 125 mg cefbutor per 10 ml
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For other Infusion in lactating dairy cattle.
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 12-10 mL (.33 Fl Oz) PLASTET® Disposable Syringes
 12 Alcohol Pads Included



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009-5279-01 4738-93/1507000 50 x 30 mm cefbutor

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