ZOETIS OFFERS THE NEWEST MASTITIS TREATMENTS. EVALUATE YOUR OPTIONS.

Brand consistency	**SPECTRAMAST® LC** *(ceftiofur hydrochloride)* Sterile Suspension	**PIRSUE®** *(pirlimycin hydrochloride)* Sterile Solution	**ToDAY®/Cefa-Lak®** (*cephapirin sodium*)	**Amoxi-Mast®** (*amoxicillin*)	**Dariclox®** (*sodium cloxacillin*)	**Hetacin-K®** (*hetacillin potassium*)
Active ingredient	Ceftiofur 125 mg	Pirlimycin 50 mg	Cephapirin 200 mg	Amoxicillin 62.5 mg	Cloxacillin 200 mg	Hetacillin potassium 62.5 mg
Indications	Treatment of clinical mastitis	Treatment of clinical and subclinical mastitis	Treatment of mastitis	Treatment of subclinical mastitis	Treatment of clinical mastitis	Treatment of acute, chronic and subclinical mastitis
Labeled pathogens	*Strep dysgalactiae* *Coagulase-negative staphylococci* *E. coli*	*Staph aureus* *Strep agalactiae* *Strep dysgalactiae* *Strep uberis*	*Strep agalactiae* *Staph aureus*	*Strep agalactiae* *Staph aureus*	*Strep agalactiae* *Staph aureus*	*Strep agalactiae* *Strep dysgalactiae* *Staph aureus* *E. coli*
Treatment/ dosing	2-8 treatments 24-hour interval	2-8 treatments 24-hour interval	2 treatments 12-hour interval	3 treatments 12-hour interval	3 treatments 12-hour interval	3 treatments 24-hour interval
Pre-slaughter withdrawal*	2 days	9 days following 2 infusions; 21 days following greater than 2 infusions	4 days	12 days	10 days	10 days
Milk discard*	72 hours	36 hours	96 hours	60 hours	48 hours	72 hours
Availability	R_X	R_X	OTC	R_X	R_X	R_X
Extended therapy	Yes	Yes	No	No	No	No

*After last administration (or treatment)

SPECTRAMAST® LC
(ceftiofur hydrochloride)
Sterile Suspension

KEY FEATURES:

- Treats *E. coli* and other major mastitis pathogens
- Once-a-day dosing — convenient for you, convenient for your milking crew
- 72-hour milk discard — residue trials show that no matter how many days you decide to treat per label directions, milk is safe for human consumption after 72 hours post-last treatment
- Two-day pre-slaughter meat withdrawal — the shortest withhold time available provides more options for greater management flexibility
- Extended therapy — its unique flexible label allows you to treat for 2 to up to 8 days to achieve a bacteriological cure

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 should not be used in animals found to be hypersensitive to the product.

PIRSUE®
(pirlimycin hydrochloride)
Sterile Solution

KEY FEATURES:

- Only lactating product for *Strep uberis*
- Unique clinical and subclinical label
- Short, 36-hour milk discard
- Once-per-day dosing
- Extended therapy — its unique flexible label allows you to treat for 2 to up to 8 days to achieve a bacteriological cure

Important Safety Information: Inappropriate dosage or treatment intervals for PIRSUE or failure to adhere to proper milk discard or meat withdrawal will result in violative milk or meat residues. As with all intramammary products, aseptic technique is essential. Repeated infusion during extended duration therapy regimens can result in elevated somatic cell counts and/or clinical mastitis, which can result in animal death. If acute clinical mastitis or other clinical signs of illness develop, discontinue therapy immediately and contact your veterinarian.

DAIRY WELLNESS MAKES A DIFFERENCE™

zoetis™

SPECTRAMAST® LC
brand of ceftiofur hydrochloride sterile suspension

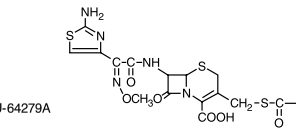
For **Intramammary** Infusion in Lactating Cows Only

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



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.

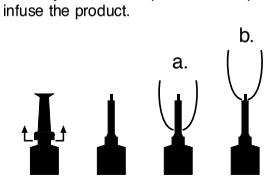
INDICATIONS FOR USE
SPECTRAMAST® LC (ceftiofur hydrochloride) Sterile Suspension is indicated for the treatment of clinical mastitis in lactating dairy cattle associated with coagulase-negative staphylococci, *Streptococcus dysgalactiae,* and *Escherichia coli*. Cows with systemic clinical signs caused 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 SPM12005
Revised May 2006 819 774 004
691273

TAKE TIME OBSERVE LABEL DIRECTIONS

Made in France.

PIRSUE® Sterile Solution
(pirlimycin hydrochloride)

For Intramammary Infusion in Lactating Cows Only

FOR USE IN ANIMALS ONLY — NOT FOR HUMAN USE

Restricted Drug — Use Only as Directed (California)

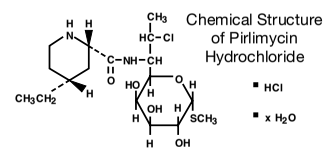
CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION
Pirlimycin hydrochloride is a lincosaminide antibiotic.

Chemical Name of Pirlimycin Hydrochloride

Methyl(2S-Cis)-7-chloro-6,7,8-trideoxy-6[[(4-ethyl-2-piperidinyl) carbonyl]amino]-1-thio-L-threo-α-D-*galacto*-octo-pyranoside monohydrochloride hydrate.

Chemical Structure of Pirlimycin Hydrochloride



PIRSUE Sterile Solution is a clear solution.

Each 10 mL PLASTET® Disposable Syringe contains:

Pirlimycin free base equivalents	50 mg
Aqueous vehicle	q.s.

INDICATIONS FOR USE
PIRSUE Sterile Solution (pirlimycin hydrochloride) is indicated for the treatment of clinical and subclinical mastitis in lactating dairy cattle associated with *Staphylococcus* species such as *Staphylococcus aureus* and *Streptococcus* species such as *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, and *Streptococcus uberis*.

DOSAGE
Infuse one (1) syringe into each affected quarter. Use proper teat end preparation and sanitation and proper intramammary infusion technique (see ADMINISTRATION). Repeat treatment after 24 hours. Daily treatment may be repeated at 24-hour intervals for up to 8 consecutive days.

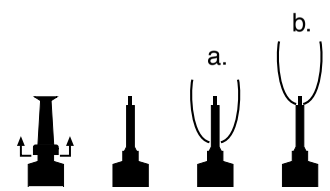
ADMINISTRATION
Teat End Preparation: Wash teats thoroughly with water containing a suitable dairy antiseptic. Dry the teats thoroughly. Milk out the udder completely. Using the alcohol pad provided, wipe the teat end of the affected quarters, using a separate pad for each teat. Allow sufficient time (at least 5 to 10 seconds) for the alcohol to dry. Use of protective gloves by persons applying treatment is recommended as part of aseptic infusion technique.

Important Considerations for Extended Therapy: For extended duration of therapy, infuse only quarters known to be infected with label pathogens. Do not concurrently infuse uninfected low SCC quarters of the same cow. Prepare the teats using the above instructions, and then infuse PIRSUE Sterile Solution using aseptic infusion technique and partial insertion (see diagram below).

Infusion: The Plastet disposable 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, R.J., et. al., 1987. Current Concepts of Bovine Mastitis, 3rd Edition, National Mastitis Council, Arlington, VA.

a. Full insertion: Remove the white end cap by pulling straight up as shown. Gently insert the full cannula into the teat canal.

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



Choose the desired insertion length (full or partial) and gently insert the tip into the teat canal. Carefully push the plunger to infuse the entire contents, and then massage the quarter to distribute the solution into the milk cistern. Following infusion, dip all quarters with an antiseptic teat dip. Cows with systemic clinical signs caused by mastitis should receive other appropriate therapy under the direction of a licensed veterinarian.

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

WARNING
Repeated infusion during extended duration therapy regimens, even with adequate teat end preparation and sanitation, can result in elevated somatic cell counts and/or clinical mastitis, which can result in animal death. If acute clinical mastitis or other clinical signs of illness develop during extended duration therapy with PIRSUE, discontinue therapy immediately and contact your veterinarian.

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

RESIDUE WARNINGS
1. Milk taken from animals during treatment and for 36 hours after the last treatment must not be used for food regardless of treatment duration.
2. Following infusion twice at a 24-hour interval, treated animals must not be slaughtered for 9 days.
3. Following any extended duration of therapy (infusion longer than twice at a 24-hour interval, up to 8 consecutive days), animals must not be slaughtered for 21 days.
4. Use of this product in a manner other than indicated under DOSAGE might result in violative residues.

PRECAUTION
When using extended duration therapy with PIRSUE Sterile Solution, failure to thoroughly clean quarters and to use aseptic infusion technique can result in the infusion of environmental mastitis pathogens not sensitive to pirlimycin.

ADVERSE REACTIONS
As demonstrated in the pivotal target animal safety study, even with adequate pre-treatment preparation, repeated infusion of PIRSUE Sterile Solution resulted in elevated SCC and clinical mastitis due to infection with Gram-negative environmental pathogens. For a complete listing of adverse reactions for pirlimycin reported to the Center for Veterinary Medicine (CVM) see http://www.fda.gov/cvm/ade_cum.htm. For technical assistance and to report suspected adverse reactions, call 1-800-366-5288. To request a Material Safety Data Sheet (MSDS), call 1-800-733-5500.

MICROBIOLOGY
Pirlimycin is a lincosaminide antibiotic that has activity against Gram-positive mastitis pathogens. Pirlimycin functions by binding to the 50S ribosomal subunit of bacterial ribonucleic acid, which interferes with protein synthesis within the bacteria. *In vitro* activity of pirlimycin has been demonstrated against *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, and *Streptococcus uberis*, four pathogens associated with clinical and subclinical mastitis in lactating dairy cattle.

Utilizing data that included isolates from cows with mastitis, zone diameter interpretive criteria and minimum inhibitory concentration (MIC) breakpoints were determined using standardized procedures from the Clinical and Laboratory Standards Institute (CLSI, formerly National Committee of Clinical Laboratory Standards) M31-A2. The CLSI-accepted interpretive criteria for pirlimycin against Gram-positive mastitis pathogens are shown in Table 1.

Table 1. CLSI-Accepted Interpretive Criteria for Pirlimycin Against Bovine Mastitis Pathogens*

Pathogen	Disk Potency	Zone Diameter Interpretive Standards (mm)		MIC Breakpoint (µg/mL)	
		Susceptible	Resistant	Susceptible	Resistant
Staphylococcus aureus *Streptococcus agalactiae* *Streptococcus dysgalactiae* *Streptococcus uberis*	2 µg	≥13	≤12	≤2.0	≥4.0

*These interpretive criteria are only intended for use when CLSI M31-A2 performance standards are used to determine antimicrobial susceptibility.

EFFECTIVENESS
The effectiveness of pirlimycin was demonstrated in a field dose response study in lactating dairy cattle with clinical mastitis. Three investigators enrolled 486 cows from 39 herds. Cows with abnormal milk (clots, flakes) and with or without udder clinical signs (swelling, redness, or soreness) were enrolled and treated, regardless of the mastitis pathogen isolated or the pre-treatment somatic cell count. Cows were treated in the affected quarter(s) with 50, 100, or 200 mg of pirlimycin twice at a 24-hour interval. A non-treated control group was included. In this study, an individual quarter was cured if it had normal milk, no udder clinical signs, and if the milk was negative for any mastitis pathogen at 10 days post-treatment. If no bacteria were isolated pre-treatment, a decrease in somatic cell count was required. A cow was cured if all enrolled quarters in that cow were cured. All three treatment levels had significantly greater cow cure rates than the non-treated control group. Based on this study, the dose of 50 mg of pirlimycin per quarter administered twice at a 24-hour interval was determined to be the effective dose for the treatment of clinical mastitis.

ANIMAL SAFETY
Two pivotal studies addressing the safety of pirlimycin administered at dosages of 50 mg or 200 mg (4X) into all four quarters twice at a 24-hour interval indicate that the formulation is safe and non-irritating to the bovine udder. Safety observations were also made during the clinical effectiveness study. No udder irritation was noted due to intramammary infusion with pirlimycin during these studies.

An additional study was conducted to determine the safety of extended duration therapy. Twenty lactating Holstein cows, first lactation or greater, at various milk production levels, and with no evidence of clinical mastitis were enrolled and treated with pirlimycin administered at a dosage of 50 mg/quarter in all four quarters daily for eight consecutive days. Cows were monitored for general health, changes in milk production and quality, and signs of udder irritation for a total of 14 days, beginning three days prior to the first treatment. Milk production was not affected by treatment. SCCs of treated cows were statistically significantly increased post-treatment relative to the pre-treatment level. A total of 24 pirlimycin-treated quarters (32%) in 15 cows had increased SCCs (>200,000 cells/mL) for at least two consecutive milkings. Of these, six treated cows (8 quarters) had a concurrent bacterial infection attributable to a mastitis pathogen. Udder irritation occurred in seven pirlimycin-treated cows (10 quarters). Abnormal strip cup scores occurred in six pirlimycin-treated cows (9 quarters). Most of the abnormal udder and strip cup observations were seen in quarters where bacteria were also isolated.

Corroborative data from field studies and field use reports indicate that although intramammary infusion of pirlimycin hydrochloride at 50 mg/quarter administered from two to eight consecutive days was well tolerated, repeated infusion with pirlimycin increases the potential for intramammary infections and subsequent clinical mastitis due to environmental bacteria, including coliform bacteria. Adverse reactions, including clinical signs of mastitis (udder swelling and abnormal milk), increased SCCs, and death from coliform mastitis have been reported in cows following extended therapy with pirlimycin. Some, but not all, adverse reactions were associated with failure to thoroughly clean quarters and to use aseptic infusion technique.

MILK AND TISSUE RESIDUE DEPLETION
The established tolerance of pirlimycin in milk is 0.40 ppm. Milk residue depletion studies were conducted in cows with clinical mastitis. In one study, cows were infused with 50 mg of pirlimycin twice at a 24-hour interval into all quarters regardless of the number of affected quarters. In a second study, cows with a single mastitic quarter were infused with 50 mg of pirlimycin twice at a 24-hour interval into only the affected quarter. In a third study, normal cows were infused with 50 mg of pirlimycin twice at a 24-hour interval into all four quarters. As a result of these three studies, milk taken from cows during treatment and for 36 hours following treatment must not be used for food and must be discarded. For extended duration of therapy (once daily for up to 8 consecutive days), a milk residue study was conducted where cows received 50 mg of pirlimycin per quarter into all four quarters for 8 consecutive days. This study confirmed that milk taken from cows during treatment and for 36 hours following the last treatment must not be used for food and must be discarded.

The established tolerance for pirlimycin in liver (the target tissue) is 0.5 ppm. A pivotal tissue residue study was conducted following administration of 50 mg of pirlimycin twice at a 24-hour interval into all four quarters. Following receipt of the 50 mg of pirlimycin twice at a 24-hour interval into all four quarters, the liver residue decline data from this study supports a 9-day pre-slaughter withdrawal period.

For extended duration of therapy, a second tissue residue study was conducted. Each lactating cow received 50 mg pirlimycin per quarter into all four quarters, once daily for 8 consecutive days. Using the established tolerance for pirlimycin of 0.5 ppm in the liver, these data support a 21-day pre-slaughter withdrawal period for extended duration pirlimycin therapy. Extended duration of therapy is considered as any treatment period longer than 2 days (up to 8 consecutive days) of therapy.

EFFECT ON MILK MANUFACTURING STARTER CULTURES
A study was conducted to examine the effect of varying concentrations of pirlimycin in milk on the growth of bacterial starter cultures used to produce fermented milk products. Pirlimycin did not adversely affect bacterial starter cultures used for the production of fermented milk products at concentrations found following normal label use including proper milk discard periods. Violative levels of pirlimycin (>0.40 ppm) can adversely affect the growth of bacterial starter cultures.

STORAGE CONDITIONS
Store at controlled room temperature 20° to 25°C (68° to77°F). Store plastets in carton or pail until used.

HOW SUPPLIED
PIRSUE Sterile Solution is available in unbroken packages of 12-10 mL Plastet Disposable Syringes with 12 individually wrapped 70% isopropyl alcohol pads. The Plastet Disposable Syringes are packaged in Cartons (12-10 mL Plastet Disposable Syringes per carton) and in Pails (12 packages of 12-10 mL Plastet Disposable Syringes or 144 Plastets per pail).

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