Date of Approval: December 12, 2007

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-036

PIRSUE Sterile Solution

Pirlimycin Hydrochloride
Lactating Dairy Cattle

For the addition of an extended duration of therapy dosage regimen.

Sponsored by:

Pharmacia & Upjohn Co.,
a Division of Pfizer, Inc.

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-036
B. Sponsor:	Pharmacia & Upjohn Co., a Division of Pfizer, Inc. 235 East 42d St. New York, NY 10017 Drug Labeler Code: 000009
C. Proprietary Name(s):	PIRSUE Sterile Solution
D. Established Name(s):	Pirlimycin hydrochloride
E. Pharmacological Category:	Antimicrobial
F. Dosage Form(s):	Sterile solution
G. Amount of Active Ingredient(s):	5 mg/mL
H. How Supplied:	10 mL plastic syringes (PLASTETS) with cannula
I. How Dispensed:	Rx
J. Dosage(s):	Infuse one (1) syringe into each affected quarter. Use proper teat end preparation and sanitation and proper intramammary infusion technique. Repeat treatment after 24 hours. **Daily treatment may be repeated at 24-hour intervals for up to 8 consecutive days.**
K. Route(s) of Administration:	Intramammary infusion
L. Species/Class(es):	Cattle (lactating dairy)

M. Indication(s):	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.*
N. Effect(s) of Supplement:	This supplement provides for an extended duration of therapy dosage regimen.

II. EFFECTIVENESS:

CVM did not require additional effectiveness studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-036 dated September 10, 1993, contains a summary of studies that demonstrate the effectiveness of pirlimycin 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*.

III. TARGET ANIMAL SAFETY:

A. Udder Irritation Study

1. Title: Milk Quality Parameters in Lactating Dairy Cows Following Eight Consecutive Daily Intramammary Infusions of PIRSUE Sterile Solution (Pirlimycin Hydrochloride). Study Report No. 1433N-60-04-429. June 2004.

2. Study Director: William M. Moseley, Ph.D. Pharmaceuticals Clinical Development, Pfizer Animal Health, Kalamazoo, MI.

3. Study Design:

   a. Objective: To assess intramammary tissue irritation using parameters associated with milk quality in normal healthy lactating dairy cows following intramammary infusion of pirlimycin hydrochloride (50 mg) into all four quarters daily for eight consecutive days.

   Except for analyses of somatic cell counts (SCCs) and feeds, the study was conducted according to Good Laboratory Practices (GLP) regulations.

   b. Test Animals: 24 healthy, lactating Holstein cows, approximately 2 to 5 years old ($\geq 1^{st}$ lactation). Cows were purchased from commercial dairies in Michigan and Wisconsin. Qualified quarters were generally free of bacterial infection, had no evidence of clinical mastitis, generally had milk SCCs of $\leq$ 200,000 cells/mL, and had no edema or teat lesions during pre-treatment milkings.

c. Treatment Groups: A total of 20 cows were assigned to receive pirlimycin in all four quarters. One cow was excluded ($\geq 2^{nd}$ lactation/high) for having a pre-existing mastitis infection. Treated cows were blocked by lactation and production as follows:

	High producer	Low producer
1^{st} lactation	$\geq$ 26.5 kg/day n = 6 cows	< 26.5 kg/day n = 6 cows
$\geq 2^{nd}$ lactation	$\geq$ 22.6 kg/day n = 3 cows	< 22.6 kg/day n = 4 cows

Four non-treated cows (all 1^{st} lactation; 3 low production, 1 high production) were included in the study but were not analyzed statistically.

d. Drug Administration: The test article was PIRSUE Sterile Solution (pirlimycin hydrochloride), containing 50 mg pirlimycin and water in a 10 mL PLASTET syringe. One tube (50 mg pirlimycin) was infused into each quarter of each cow daily for eight consecutive days (total 400 mg/quarter) beginning on Day 0.

e. Measurements and Observations: Cows were monitored during the pre-treatment (Days -3 to -1, milkings 1-6), treatment (Days 0 to 7, milkings 7-21), withdrawal (Days 7 to 8, milkings 22-24), and post-treatment (Days 9 to 14, milkings 25-36) periods. General health, rectal temperature, strip cup, composite quarter milk SCC, microbiological culture, quarter milk production, and udder palpation assessments were made from Days -3 to 14.

f. Statistical Methods: Cows in the study were assigned to blocks and treatments according to a 2 x 2 factorial design with parity and milk production being the two factors. The cow was the experimental unit. Analyses evaluated changes from pre-treatment.

SCC was averaged across milkings for each cow within each period and transformed prior to analysis via the natural logarithm (back transformed least squares means are equivalent to geometric means). Milk production was averaged across milkings for each cow within each period before analysis. Temperature was averaged within period for each cow prior to analysis. Mixed model repeated measures analyses included fixed effects of lactation, production level, lactation x production, period, period x lactation, period x production, and lactation x period x production. Random effects included animal within lactation within production level and residual.

4. <u>Results</u>:

a. General Health: Scores of "mildly depressed" were recorded for three pirlimycin treated cows on Days 7, 8, and/or 9. Non-mastitis related

abnormalities including loose stool, slightly labored breathing, and swollen feet were also reported. These observations were sporadic and did not appear to be test article-related.

b. Milk Production: Milk production for pirlimycin-treated cows was similar for each study period, as shown in the following table.

Table 1. Milk Production Results

	Pre-treatment	Treatment	Withdrawal	Post-Treatment
Milk Production (kg/cow/milking)	10.8	10.8	10.1	10.2

c. SCC: There was a significant period effect ($P < 0.04$), but no significant difference in mean SCCs associated with lactation, production, or lactation x production. Mean SCCs were statistically significantly increased in the pirlimycin-treated cows during each period relative to the pre-treatment level, as shown in the following table.

Table 2. Mean SCC Results

	Mean SCC (1000 cells/mL)			
	Pre-treatment	Treatment	Withdrawal	Post-Treatment
Pirlimycin	78	110 $P < 0.03$	181 $P < 0.03$	300 $P < 0.009$
Non-treated	32	58	90	86

Mean SCCs increased in the non-treated cows from the pre-treatment period through the withdrawal period. A total of 15 pirlimycin-treated cows (24 quarters, 32%) had elevated SCCs (> 200,000 cells/mL) for at least two consecutive milkings. In six of these cows (eight quarters), Gram-negative bacteria or yeast were isolated from the milk samples collected during the study. One of the control cows had an elevated SCC in three quarters for at least two consecutive milkings, but no bacterial pathogen was isolated.

d. Strip Cup Evaluation and Udder Irritation: Udder irritation occurred in seven pirlimycin-treated cows (10 quarters). Abnormal strip cup scores occurred in six pirlimycin-treated cows (nine quarters). There were too few abnormal observations to analyze statistically. Most of the abnormal udder and strip cup observations were seen in quarters where bacteria were isolated. None of the control cows had udder irritation or abnormal strip cup scores.

e. Rectal Temperature: In the treated and control groups, mean rectal temperature decreased during treatment, withdrawal, and post-treatment

periods relative to pre-treatment. There was no biological significance associated with the decrease.

5. Conclusion: Overall, these data indicate that administration of pirlimycin to lactating dairy cattle by intramammary infusion at 50 mg/quarter is safe. However, extended duration of therapy (administration daily for up to eight consecutive days) increases exposure of the udder to environmental bacteria as a result of the increased number of infusions. In this study, extended therapy (eight consecutive days) resulted in increased SCCs and an increased incidence of intramammary infections associated with environmental bacteria.

B. Corroborative Studies

As part of the target animal safety evaluation, CVM examined data from several corroborative effectiveness studies conducted in the United States and Europe, as well as pharmacovigilance reports submitted by the sponsor. Collectively, the data demonstrate that intramammary infusion of pirlimycin hydrochloride at 50 mg/quarter administered from two to eight consecutive days was well tolerated and will be safe for the lactating dairy cow. However, these studies also demonstrated that 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.

For a complete listing of adverse reactions for pirlimycin reported to the CVM see http://www.fda.gov/cvm/ade_cum.htm.

IV. HUMAN FOOD SAFETY:

A. Toxicology:

Complete summaries of all pivotal toxicology and metabolism studies are found in the FOI Summary for the original approval of NADA 141-036 dated September 10, 1993. For PIRSUE Sterile Solution, the no observed effect level (NOEL) (10 mg/kg from the 90 day oral rat study), the acceptable daily intake (ADI) (0.01 mg/kg/day), the safe concentrations (2.4 µg/g in liver and 0.4 µg/mL in milk), the residue marker (R_m, parent pirlimycin in liver and milk), the tolerance of parent pirlimycin (0.5 µg/g in liver and 0.4 µg/L in milk), and the regulatory methods for pirlimycin in milk and liver (high performance liquid chromatography/Thermospray/ mass spectrometry [HPLC/TSP/MS] method) remain unchanged for the pirlimycin extended therapy regimen.

An assessment performed to evaluate the safety of pirlimycin residues in food on human intestinal flora concluded that no human food safety concerns exist related to

the effect of pirlimycin residues derived from lactating dairy cows treated with an intramammary infusion at a dose level of 50 mg/quarter once daily for up to and including eight consecutive days.

B. Residue Chemistry:

1. Residue Chemistry Study

a. Title: Decline of Parent Pirlimycin Residue from the Milk and Tissues of Lactating Dairy Cattle Following Intramammary Infusion Into All Four Quarters of a Sterile Formulation of Pirlimycin Hydrochloride (PNU-57930E) at 50 mg of Free Base Equivalents/Quarter Following an Extended-Therapy Treatment Regimen of Eight Consecutive Daily Doses.

b. Study Director: R.E. Hornish, Pharmacia & Upjohn, Kalamazoo, MI.

c. Study Design:

1) Test Animals:

Animal Species:	bovine
Strain/Breed:	Holstein
Gender:	female, lactating
Number of Animals:	20 treated, 2 non-treated
Stage of Lactation:	1st-4th lactation, mid-lactation
Weight:	475-802 kg
Health Status:	healthy cows

2) Treatment Administration:

Route of Administration:	intramammary
Dose Rate:	50 mg/quarter in all 4 quarters
Duration of Dosing:	8 doses/quarter at a 24-hour interval

3) Milk Collection: 9 milkings (~108 hours) post-last-treatment

4) Sacrifice Intervals: 5 cows each on 21, 28, 35, and 42 days post-dosing

5) Pirlimycin Residue Determination: The concentration of parent pirlimycin residue in liver was determined by HPLC/TSP/MS. The concentration of parent pirlimycin residue in milk was determined by the cylinder plate microbiological assay (the results of assays of milk samples for pirlimycin using a cylinder plate microbiological assay and the regulatory HPLC/TSP/MS method have been shown to be nearly identical).

d. Results:

Depletion Data in Milk:

Table 3. Pirlimycin Residue Depletion Data in Milk

Milk concentration (Hours[1])	Concentration in μg/mL	
	Mean	Standard Deviation
12	18.6	12.2
24	1.89	1.89
36	0.45	0.33
48	0.16	0.04
60	0.12	0.05
72	0.08	0.03
84	0.08	0.03
96	0.05	0.02

[1] Time of collection post-last-treatment

Depletion Data in Liver:

Table 4. Mean Pirlimycin Residues (ppm) in Liver

Sacrifice Interval (Days)	Mean (μg/g)	Standard Deviation
21	0.032	0.021
28	0.021	0.022
35	0.028	0.018
42	<0.025	-

2. Target Tissue and Marker Residue Assignment

Parent pirlimycin is the marker residue and liver is the target tissue. Milk also must be analyzed to set the discard time. See the FOI Summary for NADA 141-036 dated September 10, 1993.

3. Tolerance Assignments

The tolerances are 0.5 μg/g in liver and 0.4 μg/mL in milk. See the FOI Summary for NADA 141-036 dated September 10, 1993.

4. Withdrawal and Milk Discard Time

The residue depletion data for liver were statistically analyzed (99th percentile tolerance limit with 95% confidence) and found to support the assignment of a

21-day withdrawal period following any extended duration of therapy (infusion longer than twice at a 24-hour interval, up to eight consecutive days). The milk-out data were similarly analyzed and determined to support the assignment of a 36-hour milk discard after the last treatment.

C. Microbial Food Safety:

The Agency evaluated the microbial food safety associated with the proposed change in duration of therapy for pirlimycin using a qualitative risk assessment procedure. This risk assessment procedure involved conducting 1) a release assessment to describe the probability that the antimicrobial new animal drug and its use in animals will result in the emergence of resistant bacteria or resistance determinants in the food animal under proposed conditions of use; 2) an exposure assessment to describe the likelihood of human exposure to the resistant bacteria or resistance determinants through consumption of edible products from treated animals, specifically, beef; and 3) a consequence assessment to describe the potential human health consequences of exposure to the defined resistant bacteria or resistance determinants by considering the human medical importance of lincosamides.

The risk of development of transferable resistance elements from this proposed new use of pirlimycin in lactating dairy cows is low. The proposed conditions of use, i.e., a dose of 50 mg per infected quarter, repeated daily for up to and including eight consecutive days for the treatment of clinical and subclinical mastitis associated with *Staphylococcus* species, such as *Staphylococcus aureus*, and *Streptococcus* species, such as *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, and *Streptococcus uberis* are compatible with the overall risk estimation of low.

D. Analytical Method for Residues:

The FOI Summary for the original approval of NADA 141-036 dated September 10, 1993, contains the regulatory method for pirlimycin in liver and milk (HPLC/TSP/MS).

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to PIRSUE Sterile Solution:

Discard empty container; do not reuse. Keep out of reach of children.

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.

VI. 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. The data demonstrate that PIRSUE Sterile Solution, when used according to the label, is safe and effective 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.* Additionally, data demonstrate that residues in food products derived from lactating dairy cattle treated with PIRSUE Sterile Solution will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

Labeling restricts this drug to use by or on 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 and subclinical mastitis, and (b) restricting this drug to use by or on order of a licensed veterinarian should help prevent indiscriminate use which could result in violative tissue residues.

B. Exclusivity:

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval. The three years of marketing exclusivity applies only to the extended duration therapy regimen for which this supplement is approved.

C. Supplemental Applications:

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR §514.106(b)(2)).

D. Patent Information:

Pirlimycin hydrochloride is under the following U.S. patent number:

U.S. Patent Number	Date of Expiration
6,648,851	March 5, 2022

VII. ATTACHMENTS:

Facsimile Labeling:

a. PIRSUE Sterile Solution – PLASTET label
b. PIRSUE Sterile Solution – carton label
c. PIRSUE Sterile Solution – pail label
d. PIRSUE Sterile Solution – package insert