Date of Approval: November 14, 2006

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-063

NUFLOR INJECTABLE SOLUTION

Florfenicol
Injectable Solution
Cattle

To add information describing florfenicol's *in vitro* bactericidal activity against some strains of *Mannheimia haemolytica* and *Histophilus somni* (*Haemophilus somnus*) to the microbiology section of the product labeling.

Sponsored by:

Schering-Plough Animal Health Corp.

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-063
B. Sponsor:	Schering-Plough Animal Health Corp. 556 Morris Ave. Summit, NJ 07901 Drug Labeler Code: 000061
C. Proprietary Name:	NUFLOR Injectable Solution
D. Established Name:	Florfenicol
E. Pharmacological Category:	Antimicrobial
F. Dosage Form:	Sterile injectable solution
G. Amount of Active Ingredient:	300 mg/mL
H. How Supplied:	100, 250, and 500 mL bottles
I. How Dispensed:	Rx
J. Dosages:	IM: 20 mg/lb body weight (3 mL/100 lbs). A second dose is administered 48 hours later. SC: 40 mg/lb body weight (6 ml/100lbs) administered once.
K. Routes of Administration:	Intramuscular and subcutaneous
L. Species/Class:	Bovine/Beef and non-lactating dairy cattle
M. Indications:	NUFLOR Injectable Solution is indicated for treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* (*Haemophilus somnus*), and for the treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*. Also, it is indicated for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*

(*Haemophilus somnus*).

N. Effect of Supplement: The effect of this supplement is to add information describing florfenicol's *in vitro* bactericidal activity against some strains of *Mannheimia haemolytica* and *Histophilus somni* to the microbiology section of the product labeling.

II. EFFECTIVENESS:

A. Dosage Characterization:

This supplemental approval does not change the previously approved dosage. The FOI Summary for the original approval of NADA 141-063 dated May 31, 1996, contains dosage characterization information for cattle.

B. Substantial Evidence:

Effectiveness of florfenicol for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* (*Haemophilus somnus*), and for the treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*, and for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica, Pasteurella multocida*, and *Histophilus somni* (*Haemophilus somnus*) was previously demonstrated in the original approval and supplemental approvals, and is summarized in the FOI Summaries for NUFLOR Injectable Solution (NADA 141-063) dated May 31, 1996; June 4, 1998; December 17, 1998; and January 14, 1999.

In vitro studies were conducted to determine florfenicol's bactericidal activity against the pathogens associated with bovine respiratory disease. Bactericidal activity was confirmed by determining the concentration of florfenicol associated with this bacterial killing activity and the duration of exposure associated with bacterial killing (defined as a 3 $\log_{10}$ reduction in colony forming units) or by establishing the MBC:MIC ratio. MBC: MIC ratio describes a relationship between the minimum *in vitro* bactericidal concentration and the MIC of an antibiotic.

If the MBC: MIC ratio of a pathogen is between 1:1 to 2:1, the drug is considered to be bactericidal against that pathogen. Alternatively, if the drug reduces the bacterial count of most strains of a pathogen by 3 $\log_{10}$ within 24 hours, this drug is classified as bactericidal for that particular pathogen. These concentrations and the duration of exposure to these concentrations need to be assessed relative to *in vivo* drug concentrations to confirm that the drug will behave as a bactericidal agent under conditions of use.

1. Microbiology Study:

a. Study Title: MBC:MIC Ration Determination for Florfenicol Against *Mannheimia Haemolytica*. Report # 46396.
February 2003 to May 2003.

b. Type of Study: MBC: MIC Ratio Determination for Florfenicol

c. Investigator: Johanne Blais, San Jose, CA

d. Study Design:

Objective: To demonstrate the bactericidal activity of florfenicol against the BRD pathogens *M. haemolytica* through minimum inhibitory concentration (MIC) and minimum bacterial concentration (MBC) determinations and comparisons.

Animals: NA

Bacterial Strains: Thirty-eight isolates of *M. haemolytica* (35 bovine, 1 ovine, and 2 laboratory strains) from North America and Europe.

Experimental Design: The determination of initial susceptibility was performed using a standard broth microdilution assay according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI). After incubation and interpretation of MIC, microtiter plates were sampled for MBC determinations by an agar dilution plate count method. MBC represents the concentration killing 99.9% (a 3 $\log_{10}$ reduction) of the initial inoculum.

e. Results:

Table 1: *In Vitro* Activity of Florfenicol

	MIC (/mL)			MBC (/mL)		
	Range	MIC_{50}	MIC_{90}	Range `	MBC_{50}	MBC_{90}
M. haemolytica	< 0.25 – 2	0.5	1	0.25 – 4	1	1

Table 2: Distribution of Florfenicol MBC:MIC Ratios

	M. haemolytica	
MBC:MIC	N	Cumulative %
1	20	53
2	17	97
≥ 2	1	100

f. Conclusion: The MIC and MBC results and the ratios of the two indicate that florfenicol exhibits bactericidal activity against strains of *M. haemolytica*.

2. Microbiology Study:

a. Study Title: *In vitro* Evaluation of the Kinetics of the Bactericidal Effect of Florfenicol Against *Haemophilus somnus*. Study No. X00-206-01. December 2000 to January 2001.

b. Type of Study*:* Kinetics study

c. Investigator: M. Bonnier, Rennes, France

d. Study Design:

Objective: To characterize the pharmacodynamic properties of florfenicol against the pathogenic BRD organism of cattle, *Histophilus somni* (*Haemophilus somnus*) by studying the effects of concentration and time of exposure to the antibiotic.

Animals: NA

Bacterial Strains: Four field isolates of *H. somni* isolated from cattle with respiratory disease and one ATCC reference strain.

Antibiotic: Florfenicol at the following concentrations: 0, 0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, and 16.0 µg/mL.

Experimental Design: The organisms were incubated for 18 hours at 37°C, 6% CO_2, in the appropriate medium. Inocula were standardized by measuring the optical density of the broth culture and adjusted to obtain 10^7 CFU/mL. The experiments were conducted in microtitre plates with 96 wells containing adequate dilutions of florfenicol.

A bacterial count was carried out immediately after the inoculation of the plates from the microbial suspension sampled from the first row of wells. The plates were placed in an incubator and the next seven rows were counted after seven incubation periods (1, 2, 4, 6, 8, 10, and 24 hours). The suspensions were sampled in each well of the corresponding row at the different times and transferred into the wells of the first row of a sterile microtitre plate where serial ten-fold dilutions were carried out. Viability counts were performed by plating onto agar (in triplicate) these seven serial 10-fold dilutions of each concentration. The number of colonies formed at each deposit was counted after incubation of the plates.

e. Results: A 3 $\log_{10}$ reduction in colony counts (99.9% kill rate) was demonstrated for the ATCC reference strain and three of four field isolates of *H. somni* by eight hours of exposure to 0.5 µg/mL florfenicol (1XMIC_{90}). The 3 $\log_{10}$ reduction in the fourth field isolate occurred by 10 hours of exposure to 0.5 µg/mL florfenicol (1XMIC_{90}).

f. Conclusion: This study demonstrates that florfenicol exhibits bactericidal activity against strains of *H. somni*. At concentrations of 0.5 µg/mL, which corresponds to 1X MIC, florfenicol reduced viable counts by more than three logs within eight hours for 80% of the isolates and within 10 hours for 100% of the isolates.

3. Pharmacokinetic Study:

a. Study Title: *In vivo* evaluation of the pharmacokinetic profile of NUFLOR when dosed at a rate of 40 mg/kg body weight (BW) via subcutaneous (SC) injection in the cervical (neck) region. Study No. 03370.

b. Type of Study: Pharmacokinetic study

c. Study Location:

In-life phase: SPAH, Terre Haute IN.
Analytical phase: Schering Plough, Lafayette, NJ.

d. Study Design:

Objective: To determine the pharmacokinetic profile of NUFLOR Injectable Solution administered subcutaneously in the neck at a dose of 40 mg/kg BW.

Animals: Twenty-four beef cattle (12 males and 12 females) weighing 170 – 346 kg.

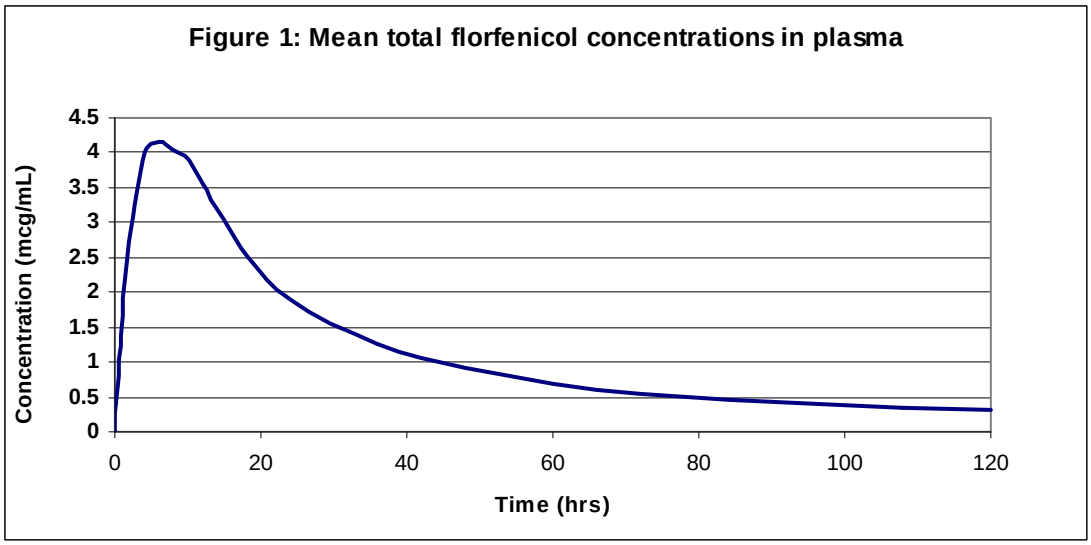
Animals were housed in an indoor barn and were segregated into two pens (one for each sequence group).

Antimicrobial: NUFLOR Injectable Solution was administered at a dose of 40 mg/kg BW subcutaneously.

Experimental Design: At each sampling time, approximately 10 mL of blood was collected via jugular venipuncture. EDTA was used as an anticoagulant. Samples for analysis were shipped to the analytical facility at the end of the in-life portion of the investigation. Concentrations of florfenicol were measured by a validated liquid chromatographic mass spectrometry (LS-MS/MS) method with a limit of quantification (LOQ) of 0.05 µg/mL.

e. Results:

A graph of the mean concentration versus time profile is provided in Figure 1.



Based upon this graph, we see that average drug concentrations are maintained above 2 µg/mL for longer than 12 hours and above 1 µg/mL for longer than 24 hours. These concentrations are consistent with the necessary duration of exposure to achieve a 3-$\log_{10}$ decrease in colony forming units of *Histophilus somni*, as demonstrated in the *in vivo* time/kill studies.

Additional study data indicated that bactericidal activity against *Mannheimia haemolytica* was observed when florfenicol concentrations are at or above 2 µg/mL for 8 hours.

f. Conclusion: The NUFLOR concentration/time profile is consistent with bactericidal activity against strains of both *Histophilus somni* and *Mannheimia haemolytica* when NUFLOR is administered at a dose of 40 mg/kg BW via subcutaneous injection.

III. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-063 dated May 31, 1996, and a supplemental approval dated June 4, 1998, contains a summary of target animal safety studies for cattle.

IV. HUMAN FOOD SAFETY:

A. Toxicology:

CVM did not require toxicology studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-063 dated May 31, 1996, contains a summary of all toxicology studies.

B. Residue Chemistry:

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-063 dated May 31, 1996, and a supplemental approval dated June 4, 1998, contains a summary of residue chemistry studies for cattle.

C. Microbial Food Safety:

The impact of adding information to the microbiology section of the product labeling stating that florfenicol exhibits bactericidal activity against some strains of the bovine respiratory disease (BRD) pathogens *Mannheimia haemolytica* and *Histophilus somni* (formerly *Haemophilus somnus*) was carefully considered by the Agency. The Agency determined that this addition to the microbiology section of the product labeling should not significantly impact public health, and therefore an evaluation of microbial food safety regarding this change was not necessary at this time.

D. Analytical Method for Residues:

The FOI Summary for the original approval of NADA 141-063 dated May 31, 1996, and supplemental approval dated June 4, 1998, contains the analytical method summaries for florfenicol in cattle.

V. USER SAFETY:

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

Not for human use. Keep out reach of children. This product contains materials that can be irritating to skin and eyes. Avoid direct contact with skin, eyes, and clothing. 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. Consult a physician if irritation persists. Accidental injection of this product may cause local irritation. Consult a physician immediately. The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information.

For customer service, adverse effects reporting, and/or a copy of the MSDS, call 1-800-211-3573.

The user safety information as listed on the product label is acceptable.

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 NUFLOR Injectable Solution, when used according to the label, is safe and effective for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* (*Haemophilus somnus*), and

for the treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*. Also, it is indicated for the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica, Pasteurella multocida,* and *Histophilus somni* (*Haemophilus somnus*). Additionally, data demonstrate that residues in food products derived from cattle treated with NUFLOR Injectable 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 BRD or foot rot, 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:

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

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)(1)).

D. Patent Information:

The sponsor did not submit any patent information with this application.

VII. ATTACHMENTS:

Facsimile Labeling:
NUFLOR (florfenicol) Injectable Solution 100 mL carton label
NUFLOR (florfenicol) Injectable Solution 100 mL package insert
NUFLOR (florfenicol) Injectable Solution 100 mL bottle label
NUFLOR (florfenicol) Injectable Solution 250 mL bottle expandable label
NUFLOR (florfenicol) Injectable Solution 500 mL bottle expandable label