Date of Approval: January 14, 1999

FREEDOM OF INFORMATION SUMMARY

NADA 141-063

NUFLOR® Injectable Solution

(florfenicol)

"...for the treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*"

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

Sponsored by:

Schering-Plough Animal Health

I. GENERAL INFORMATION

NADA Number:	141-063
Sponsor:	Schering-Plough Animal Health Corporation 1095 Morris Avenue Union, New Jersey 07083
Generic Name:	florfenicol
Trade Name:	NUFLOR® Injectable Solution
Marketing Status:	A prescription (Rx) product which carries the following caution statement: "Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian."
Supplemental Effect:	Provides for the use of florfenicol (NUFLOR® Injectable Solution) for treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus.*

II. INDICATIONS FOR USE

NUFLOR® Injectable Solution (florfenicol) is indicated for the treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus.*

III. DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE

A. Dosage Form

NUFLOR® Injectable Solution is a sterile non-aqueous solution available in 100-, 250-, and 500-mL glass vials. Each milliliter contains 300 mg florfenicol.

NUFLOR® Injectable Solution should be stored between 2 to 30 °C (36 to 86 °F). Refrigeration is not required. The solution is light yellow to straw colored. Color does not affect potency.

B. Route of Administration

NUFLOR® Injectable Solution should be administered to cattle by intramuscular or subcutaneous injection in the neck.

C. Recommended Dosage

NUFLOR® Injectable Solution should be administered by intramuscular injection to cattle at a dose rate of 20 mg/kg body weight (3 mL/100 lbs). A second dose should be administered 48 hours later. Alternatively, NUFLOR® Injectable Solution can be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (6 mL/100 lbs). Do not administer more than 10 mL at each site. The injection should be given only in the neck.

IV. EFFECTIVENESS

An original new animal drug application (NADA) for NUFLOR® Injectable Solution (NADA 141-063) for intramuscular administration to cattle for the treatment of bovine respiratory disease was approved May 31, 1996. On June 4, 1998, NUFLOR® Injectable Solution was approved for the treatment of bovine respiratory disease (BRD) associated with *Pasteurella haemolytica, Pasteurella multocida*, and *Haemophilus somnus* by a single subcutaneous injection of 40 mg/kg body weight. Dose range-finding studies and field trials conducted for the original NADA and the alternative subcutaneous route of administration are summarized in the respective Freedom of Information Summaries (FOIs).

Pivotal Studies (2) for this Supplemental NADA

A. Challenge Model Study

1. Type of Study: clinical effectiveness with induced infections

2. Investigator: John Berg, D.V.M., Ph.D.
University of Missouri-Columbia
College of Veterinary Medicine
Columbia, Missouri 65211

3. General Design: Prospective, randomized and controlled; 3 treatment groups.

   a. Purpose: To evaluate the clinical efficacy of florfenicol administered: 1) IM at 20 mg/kg, dosed twice at a 48-hour interval; and 2) SC at 40 mg/kg, dosed once, in an induced model of bovine interdigital necrobacillosis (intradermal inoculation of *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*) compared to non-medicated controls.

   b. Animals: Forty-eight calves total, approximately 6 months of age, average weight 255 kg

   c. Control: Negative control (sterile water; route and volume equivalent to NUFLOR® IM at 20 mg/kg, dosed twice at a 48-hour interval)

   d. Dosage Form: NUFLOR® Injectable Solution, 300mg/mL

   e. Route of Administration and Dose: Intramuscular (IM) injection, or subcutaneous (SC) injection; IM at 20 mg/kg, dosed twice at a 48-hour interval (Days 0 and 2); SC at 40 mg/kg, once (Day 0). Injections were limited to a 10 mL volume per site.

   f. Test Duration: Eleven days

   g. Pertinent Parameters Measured: Calves were treated on Day 0 for acute bovine foot rot. Foot rot was induced in three feet per calf by interdigital, intradermal inoculation of a mixed culture of *Fusobacterium necrophorum* and *Bacteroides melaninogenicus* administered on Day -3. Feet were enrolled based on lesion severity.

Lesion and lameness severity were assessed on Days 0, 2, 4, 7, and 11. Criteria for scoring of lesions and lameness are shown in Tables 4.1 and 4.2.

Table 4.1. Lesion interpretation

Score*	Interpretation
0	No lesion or swelling
1	Small lesion visible with no swelling; or no lesion with slight to moderate swelling present
2	Severe swelling with no lesion; or slight swelling with small interdigital necrotic lesion
3	Small to medium size necrotic lesion with moderate to severe swelling
4	Very large lesion with slight swelling; or medium size necrotic lesion extending about 1/3 to 1/2 the length of the interdigital space with severe swelling
5	Very large necrotic lesions (extending almost full length of interdigital space); moderate to severe swelling present

*Extension of the infection into the joints was graded as a 4 or 5 depending on the severity of the lesions.

Table 4.2. Lameness interpretation

Score	Interpretation
0	Normal
1	Slight lameness
2	Moderate lameness
3	Severe to very severe lameness

Treatment success or improvement was determined on Day 7 and Day 11 based on lesion scores compared to Day 0. The following criteria were used:

Success: Day 0 lesion score of at least 2 decreases to a lesion score of 0 or 1; or Day 0 lesion score of 1 decreases to a lesion score of 0.

Improved: Day 0 lesion score of at least 3 decreases to a lesion score of 2.

Failure: Calves not meeting the above criteria.

4. Results: Calves receiving NUFLOR® (IM or SC) demonstrated a steady decline in mean lesion score from Day 0 to Days 2, 4, 7, and 11 (Table 4.3). Lesion scores for calves in the NUFLOR® IM and SC groups were significantly lower than calves receiving no antibiotic at all time points. Similarly for lameness,

calves receiving NUFLOR® (IM or SC) were significantly less lame than unmedicated calves at each evaluation after initiation of drug therapy (Table 4.4). With the exception of Day 4, the IM and SC NUFLOR® groups were clinically and statistically equivalent for mean lesion and mean lameness scores.

Table 4.3. Mean lesion scores, by treatment group by day

Day	Unmedicated (n=45)*	NUFLOR® IM (n=48)*	NUFLOR® SC (n=45)*
0	2.76	2.90	2.67
2	3.31	2.42	2.56
4	2.49	1.67	2.02
7	2.44	0.85	0.91
11	1.67	0.35	0.51

*n refers to the number of feet per treatment group

Table 4.4. Mean lameness scores, by treatment group by day

Day	Unmedicated (n=44)*	NUFLOR® IM (n=48)*	NUFLOR® SC (n=41)*
0	1.91	1.71	1.80
2	1.70	1.02	1.12
4	1.25	0.40	0.76
7	1.55	0.33	0.39
11	0.93	0.19	0.07

*n refers to the number of feet per treatment group

Treatment efficacy for each foot was evaluated as the change in mean lesion score from Day 0 to Day 7, and Day 0 to Day 11. On Day 7, treatment success was declared for 81% of animals in the NUFLOR® IM group, 78% in the NUFLOR® SC group, and 27% in the unmedicated group. Lesion resolution continued to Day 11, as success rates were 94% in the NUFLOR® IM group, 89% in the NUFLOR® SC group, and 51% in the unmedicated group ($p<0.0001$).

5. Statistical Analysis: All three clinical variables (lesion scores, lameness scores, and treatment success) were ordered categorically and scored for each foot. The ordered categorical results were analyzed by a Nested Analysis of Covariance (ANCOVA; foot nested in calf). For all analyses, statistical significance was declared when $p\leq0.05$ and preliminary significance when $0.05<p<0.10$. Each Day (0, 2, 4, 7, 11) was separately evaluated.

6. Conclusion: NUFLOR® administered to cattle intramuscularly at 20 mg/kg, twice at a 48-hour interval, or subcutaneously at 40 mg/kg once, is an effective therapeutic regimen compared to no antibiotic in an induced model of bovine foot rot (interdigital necrobacillosis).

B. Field Study

1. Type of Study: Clinical effectiveness

2. Investigators: Kelly Lechtenberg, D.V.M., Ph.D.
Midwest Veterinary Services
1443 Highway 77
Oakland, Nebraska 68045

3. General Design: Prospective, randomized and controlled; 3 treatment groups.

a. Purpose: To evaluate the clinical efficacy of florfenicol administered: 1) IM at 20 mg/kg, dosed twice at a 48-hour interval; and 2) SC at 40 mg/kg, dosed once, for naturally-occurring acute, bovine interdigital necrobacillosis (foot rot) compared to non-medicated controls.

b. Animals: Ninety crossbred steers (beef); at least 6 months old; mean weight 436 kg (range 336 to 518 kg).

c. Control Group: Negative control (sterile saline for injection; route and volume equivalent to NUFLOR® IM at 20 mg/kg, dosed twice at a 48-hour interval).

d. Dosage Form: NUFLOR® Injectable Solution, 300mg/mL

e. Route of Administration and Dose: Intramuscular (IM) injection, or subcutaneous (SC) injection; IM at 20 mg/kg, dosed twice at a 48-hour interval (Days 0 and 2); SC at 40 mg/kg, once (Day 0). Injections were limited to a 10 mL volume per site.

f. Test Duration: Seven days

g. Pertinent Parameters Measured: Calves were treated on Day 0 for naturally occurring, acute, bovine foot rot. Feet were enrolled based on two consecutive days of non-resolving lesions and lameness. In order to be enrolled, cattle had to exhibit clinical signs of foot rot as defined as lesion and lameness scores ≥2 in at least one foot on two consecutive days. Lesion and lameness severity were assigned on Days -1, 0, 2, 4, and 7. Criteria for scoring of lesions and lameness are shown in Tables 4.5 and 4.6.

Table 4.5. Lesion interpretation

Score	Interpretation
0	No lesion or swelling
1	No lesion visible; slight to moderate swelling present
2	Severe swelling with no lesion; or slight swelling with small interdigital necrotic lesion
3	Small to medium size necrotic lesion with moderate to severe swelling
4	Large to very large interdigital necrotic lesion (near full length to full length of interdigital space) with moderate to severe swelling

Table 4.6. Lameness interpretation

Score	Interpretation
0	Normal
1	Slight lameness
2	Moderate lameness
3	Severe lameness

Treatment success, improvement, or failure was determined on Day 7 based on lesion scores and lameness compared to Day 0. The following criteria were used:

Success: Day 0 lesion score ≥2 decreasing to a lesion score of 0 or 1; with a corresponding reduction in lameness score of at least 2 points.

Improved: Day 0 lesion score ≥3 decreasing to a lesion score of 2, with a corresponding reduction in lameness score of at least 2 points, or a lameness score returning to zero.

Failure: Calves not meeting the above criteria for treatment success or improvement.

4. Results: NUFLOR® IM and SC groups were clinically and statistically more effective than saline treatment in reducing lesion (Table 4.7) and lameness (Table 4.8) severity. The two NUFLOR® groups were clinically and statistically equivalent throughout the study.

Table 4.7. Lesion scores, by treatment group by day, for cattle treated for foot rot with NUFLOR® (florfenicol) by intramuscular (IM) or subcutaneous (SC) injection compared to saline control.

Day	Treatment*	Lesion Score				
		0	1	2	3	4
0	saline	--	--	10	20	0
	Nuflor® IM	--	--	10	20	0
	Nuflor® SC	--	--	9	21	0
2	saline	0	1	13	15	1
	Nuflor® IM	2	13	15	0	0
	Nuflor® SC	1	10	18	1	0
4	saline	0	1	15	14	0
	Nuflor® IM	11	13	6	0	0
	Nuflor® SC	3	23	3	1	0
7	saline	0	0	16	13	1
	Nuflor® IM	16	9	5	0	0
	Nuflor® SC	12	13	4	1	0

*n was equal to 30 at each time point for each treatment group

Table 4.8. Lameness scores, by treatment group by day, for cattle treated for foot rot with NUFLOR® (florfenicol) by intramuscular (IM) or subcutaneous (SC) injection compared to saline control.

Day	Treatment*	Lameness Score			
		0	1	2	3
0	saline	--	--	6	24
	Nuflor® IM	--	--	5	25
	Nuflor® SC	--	--	7	23
2	saline	0	0	10	20
	Nuflor® IM	4	9	16	1
	Nuflor® SC	1	12	17	0
4	saline	0	2	12	16
	Nuflor® IM	11	11	8	0
	Nuflor® SC	11	11	7	1
7	saline	0	2	10	18
	Nuflor® IM	19	7	4	0
	Nuflor® SC	19	6	3	2

*n was equal to 30 at each time point for each treatment group

Treatment efficacy for affected feet was evaluated as the change in lesion and lameness scores from Day 0 to Day 7. The treatment success rate in each Nuflor® group was 77% compared to 0% in the saline group.

Twenty-five lesions were cultured, yielding 23 isolates of both *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*. Florfenicol MIC_{50} and MIC_{90} for both organisms were 0.25 µg/mL.

5. Statistical Analysis: Lesion scores, lameness scores, and treatment success were all ordered categorical variables and were analyzed by the Kruskal-Wallis Test. For all analyses, statistical significance was declared when $p \leq 0.05$ and preliminary significance when $0.05 < p < 0.10$.

6. Conclusion: NUFLOR® administered to cattle intramuscularly at 20 mg/kg, twice at a 48-hour interval, or subcutaneously at 40 mg/kg once, is an effective therapeutic regimen compared to no antibiotic in naturally-occurring, acute, bovine foot rot (interdigital necrobacillosis).

C. Determination of Mean Inhibitory Concentrations (MICs) of Florfenicol

F. necrophorum and *B. melaninogenicus* isolates collected from naturally occurring interdigital phlegmon cases from 1973 to 1997 in the United States were analyzed to determine the MICs of florfenicol. A summary of the results is shown in Table 4.9. Of the 23 isolates (12 *F. necrophorum* and *11 B. melaninogenicus*) collected from clinical cases of acute bovine foot rot during 1997, no isolate had an MIC greater than 0.25 µg/mL.

Table 4.9. MIC values of florfenicol against bacterial isolates collected from 1973 to 1997 from natural infections of cattle (n=53).

Bacteria	No. of Isolates	MIC Range (µg/mL)	MIC_{50}* (µg/mL)	MIC_{90}** (µg/mL)
F. necrophorum	33	0.125 to 0.5	0.25	0.25
B. melaninogenicus	20	0.125 to 0.25	0.25	0.25

* Minimum inhibitory concentration for 50% of the isolates
**Minimum inhibitory concentration for 90% of the isolates

V. ANIMAL SAFETY

The supplemental approval for this new indication does not change the dose of florfenicol, the frequency, or route of administration. Accordingly, no additional studies were required for animal safety. See the Freedom of Information (FOI) Summaries for the approval of the original and supplemental applications of NUFLOR® Injectable Solution (NADA # 141-063), approved May 31, 1996, and June 4, 1998.

VI. HUMAN SAFETY

The supplemental approval for this new indication does not change the dose of florfenicol, the frequency, or route of administration. Accordingly, no additional studies were required for human food safety. See the Freedom of Information (FOI) Summaries for the approval of the original and supplemental applications of NUFLOR® Injectable Solution (NADA # 141-063), approved May 31, 1996, and June 4, 1998.

VII. AGENCY CONCLUSIONS

The data submitted in support of this NADA supplement 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 florfenicol, when administered as an intramuscular injection at 20 mg/kg, dosed twice at a 48-hour interval, or as a single subcutaneous injection at 40 mg/kg, is safe and effective for the treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus.*

Labeling restricts this drug to use by or on order of a licensed veterinarian. The Center for Veterinary Medicine (CVM) has concluded that this product shall continue to have prescription marketing status.

The agency has determined under 21 CFR 25.33(d)(5) that this action is of the type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Under the Center's supplemental approval policy (21 CFR 514.106(b)(2)(v)), this is a Category II change. The approval of this change is not expected to have any adverse effect on the safety or effectiveness of this new animal drug and, therefore, did not require a reevaluation of the human food or target animal safety data in the parent application.

Under Section 512(c)(2)(F)(iii) of the FFDCA, this approval for food-producing animals qualifies for THREE (3) years of marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or, in the case of food producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the addition of the new indication, treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus,* for which the supplemental application is approved.

NUFLOR® Injectable Solution is under U.S. patent number 5,082,863, which expires January 21, 2009.

VIII. APPROVED LABELING

A copy of the draft facsimile labeling is attached to this document.

A. NUFLOR® Injectable Solution - Vial Labels

B. NUFLOR® Injectable Solution - Carton Label

C. NUFLOR® Injectable Solution - Package Inserts