Date of Approval: 12/17/98

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-063

NUFLOR® Injectable Solution

(florfenicol)

"...for the control of respiratory disease in cattle at high risk of developing bovine respiratory disease (BRD) associated with *Pasteurella haemolytica, Pasteurella multocida*, and *Haemophilus somnus*"

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) as a single subcutaneous injection in cattle at high risk of developing bovine respiratory disease (BRD).

II. INDICATIONS FOR USE

NUFLOR® Injectable Solution (florfenicol) is indicated for the control of respiratory disease in cattle at high risk of developing bovine respiratory disease (BRD) associated with *Pasteurella haemolytica, Pasteurella multocida*, and *Haemophilus somnus.*

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

For the above stated indication, NUFLOR® Injectable Solution should be administered to cattle by subcutaneous injection in the neck.

C. Recommended Dosage

NUFLOR® Injectable Solution should 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. Field Trial: Study # 1320E-61-V96-308-01, Report # A-27712

1. Type of Study: Clinical effectiveness

2. Investigators: Dr. Kelly Lechtenberg & Dr. A. Edwards
Midwest Veterinary Services
1443 Highway 77
Oakland, Nebraska 68045

3. General Design:

a. Purpose: To evaluate the clinical effectiveness of florfenicol administered by subcutaneous injection (SC) at 40 mg/kg, dosed once, on the incidence of morbidity and mortality due to BRD in high risk cattle as compared to a negative control (unmedicated).

b. Animals: A total of 399 beef crossbred heifer calves; 6 months of age or older; mean weight 242 kg (range of 148 to 314 kg)

c. Control: Negative control (unmedicated)

d. Treatment groups: The treatment groups are shown in Table 4.1.

Table 4.1. Treatment groups

Group	Number of Animals	Day 0 Rectal Temp (°F)
NUFLOR® SC @ 40 mg/kg	200	102.3
Untreated	199	102.4

e. Diagnosis: Recently arrived feeder cattle were processed as per the practice of the feedlot, weighed, and their rectal temperatures were taken. Calves exhibiting acute clinical signs of BRD, musculoskeletal disease, or other systemic disease that precluded successful completion of the 28-day

study period were not eligible for inclusion into the study. Calves were observed for BRD incidence from Day 1 to Day 28. Morbidity was based on clinical appearance, rectal temperature, respiratory rate, dyspnea, cough, and nasal discharge. Cases of BRD and mortalities attributed to BRD after initial treatment on Day 0, but prior to therapeutic intervention, were declared "treatment failures."

f. Dosage Form: The dosage form was an injectable solution containing 300 mg florfenicol per mL.

g. Route of Administration: Subcutaneous injection in the neck region.

h. Dose: 40 mg florfenicol/kg body weight administered once.

i. Test Duration: Twenty-eight (28) days.

j. Pertinent Parameters Measured: The primary parameter for determination of efficacy was reduction of morbidity.

4. Statistical Analysis: The pivotal variable for clinical evaluation was the proportion of cattle breaking with BRD per treatment group (cattle treated for BRD or mortality due to BRD following Day 0). Analysis was by the Fisher's Exact Test. The mean time to first break with BRD was analyzed by a one-sided T-test. The median time to first break was reported and analyzed by the Wilcoxon Exact Rank Sum Test. Initial rectal temperatures and body weights taken on Day 0 were analyzed by ANOVA.

   Individual calves were the experimental unit for all analyses. The results of all statistical tests were declared significant at the alpha = 0.05 level. Preliminary statistical significance was declared when $0.05 < \alpha < 0.10$. All analyses were one-tailed tests, since the comparison was to a negative control.

5. Results: The effects of florfenicol on morbidity and mortality are summarized in Table 4.2.

   Table 4.2. Morbidity and mortality due to BRD in high risk calves following a single SC injection of florfenicol prior to evidence of clinical signs of BRD

Group	BRD Morbidity*	Mean Days Until BRD Developed	Median Days Until BRD Developed	Mortalities
NUFLOR®	3 (6/200)	12.5	11	0
Untreated	9 (18/199)	8.5	9	0

*Represents percentage of animals that contracted BRD

In the NUFLOR® group, 6 of the 200 calves (3%) met the protocol definition of treatment failure by developing BRD following treatment on Day 0. This was statistically significantly lower than the 18 treatment failures (9%) in the unmedicated group (p=0.0091). Among calves that developed BRD, the mean

time to first incidence of BRD (from Day 0; mean time in days for the first BRD break) was 12.5 days in the NUFLOR® group; the median time was 11 days. In contrast, the unmedicated group had a mean time of 8.5 days to first incidence of BRD, and a median time of 9 days. The 4-day difference between the two groups for mean time to first incidence of BRD was preliminarily statistically significant (p=0.0540). Median times (11 days vs. 9 days) were not statistically different. No adverse reactions following administration of NUFLOR® were reported.

6. Conclusion: These data demonstrate that NUFLOR® Injectable Solution, administered by subcutaneous injection (40 mg/kg body weight), is effective for the control of respiratory disease in cattle at high risk of developing BRD associated with *Pasteurella haemolytica, Pasteurella multocida*, and *Haemophilus somnus.*

B. Field Trial: Study # 1320E-61-V96-308-02, Report # A-27713

1. Type of Study: Clinical effectiveness

2. Investigators: Dr. G. Weaver & Dr. J. McWhirter
Sheldon Associates
2414 Lakeview, Suite 8
Amarillo, Texas 79109

3. General Design:

a. Purpose: To evaluate the clinical effectiveness of florfenicol administered by subcutaneous injection (SC) at 40 mg/kg, dosed once, on the incidence of morbidity and mortality due to BRD in high risk cattle as compared to a negative control (unmedicated).

b. Animals: A total of 198 beef crossbred heifer calves; 6 months of age or older; mean weight 226 kg (range of 183 to 298 kg)

c. Control: Negative control (unmedicated)

d. Treatment groups: The treatment groups are shown in Table 4.3.

Table 4.3. Treatment groups

Group	Number of Animals	Day 0 Rectal Temp (°F)
NUFLOR® SC @ 40 mg/kg	99	102.4
Untreated	99	102.4

e. Diagnosis: Recently arrived feeder cattle were processed as per the practice of the feedlot, weighed, and their rectal temperatures were taken. Calves exhibiting acute clinical signs of BRD, musculoskeletal disease, or other systemic disease that precluded successful completion of the 28-day

study period were not eligible for inclusion into the study. Calves were observed for BRD incidence from Day 1 to Day 28. Morbidity was based on clinical appearance, rectal temperature, respiratory rate, dyspnea, cough, and nasal discharge. Cases of BRD and mortalities attributed to BRD after initial treatment on Day 0, but prior to therapeutic intervention, were declared "treatment failures."

f. Dosage Form: The dosage form was an injectable solution containing 300 mg florfenicol per mL.

g. Route of Administration: Subcutaneous injection in the neck region.

h. Dose: 40 mg florfenicol/kg body weight administered once.

i. Test Duration: Twenty-eight (28) days.

j. Pertinent Parameters Measured: The primary parameter for determination of efficacy was reduction of morbidity.

4. Statistical Analysis: The pivotal variable for clinical evaluation was the proportion of cattle breaking with BRD per treatment group (cattle treated for BRD or mortality due to BRD following Day 0). Analysis was by the Fisher's Exact Test. The mean time to first break with BRD was analyzed by a one-sided T-test. The median time to first break was reported and analyzed by the Wilcoxon Exact Rank Sum Test. Initial rectal temperatures and body weights taken on Day 0 were analyzed by ANOVA.

   Individual calves were the experimental unit for all analyses. The results of all statistical tests were declared significant at the alpha = 0.05 level. Preliminary statistical significance was declared when $0.05 < \alpha < 0.10$. All analyses were one-tailed tests since the comparison was to a negative control.

5. Results: The effects of florfenicol on morbidity and mortality are summarized in Table 4.4.

   Table 4.4. Morbidity and mortality due to BRD in high risk calves following a single SC injection of florfenicol prior to evidence of clinical signs of BRD

Group	BRD Morbidity*	Mean Days Until BRD Developed	Median Days Until BRD Developed	Mortalities
NUFLOR®	67 (66/99)	15.7	15	2
Untreated	81 (80/99)	7.0	4	0

*Represents percentage of animals that contracted BRD

In the NUFLOR® group, 66 of the 99 calves (67%) met the protocol definition of treatment failure by developing BRD following treatment on Day 0. This was statistically significantly lower than the 80 treatment failures (81%) in the unmedicated group (p=0.0176). Among calves that developed BRD, the mean

time to first incidence of BRD (from Day 0; mean time in days for the first BRD break) was 15.7 days in the NUFLOR® group; the median time was 15 days. In contrast, the unmedicated group had a mean time of 7 days to first incidence of BRD, and a median time of 4 days. The 8.7-day difference between the two groups for mean time and the 11 day difference in median time to first incidence of BRD were both statistically different ($p<0.0001$). No adverse reactions following administration of NUFLOR® were reported.

Two animals treated with florfenicol died of BRD after diagnosis and removal from the group, but before other antibiotic treatment was initiated. These two deaths occurred on Day 15 of the study. There were also four additional deaths (one calf in the untreated group and three florfenicol treated calves). The additional four deaths occurred between Day 21 and Day 25 of the study after therapeutic intervention had been initiated and are not included in the "Mortalities" column of Table 4.4 above.

6. Conclusion: These data demonstrate that NUFLOR® Injectable Solution, administered by subcutaneous injection (40 mg/kg body weight), is effective for the control of respiratory disease in cattle at high risk of developing BRD associated with *Pasteurella haemolytica, Pasteurella multocida*, and *Haemophilus somnus.*

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, respectively.

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, respectively.

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 a single subcutaneous injection at 40 mg/kg, is safe and effective for the control of respiratory disease in cattle at high risk of developing BRD associated with *Pasteurella haemolytica, Pasteurella multocida*, and *Haemophilus somnus.*

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, control of respiratory disease in cattle at high risk of developing BRD associated with *Pasteurella haemolytica, Pasteurella multocida*, and *Haemophilus somnus*, 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