

NADA #141-063, Approved by FDA.

Nuflor®
(FLORFENICOL)

Injectable Solution
300 mg/mL

For Intramuscular and Subcutaneous Use in Cattle Only.

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

DESCRIPTION NUFLOR Injectable is a solution of the synthetic antibiotic florfenicol. Each milliliter of sterile NUFLOR Injectable Solution contains 300 mg of florfenicol, 250 mg n-methyl-2-pyrrolidone, 150 mg propylene glycol, and polyethylene glycol qs.

CLINICAL PHARMACOLOGY The pharmacokinetic disposition of NUFLOR Injectable Solution was evaluated in feeder calves following single intramuscular administration at the recommended dose of 20 mg/kg. NUFLOR Injectable Solution was also administered intravenously to the same cattle in order to calculate the volume of distribution, clearance, and percent bioavailability* (Table 1).

TABLE 1. Pharmacokinetic Parameter Values for Florfenicol Following IM Administration of 20 mg/kg Body Weight to Feeder Calves (n=10).

Parameter	Median	Range
C _{max} (µg/mL)	3.07*	1.43 - 5.60
T _{max} (hr)	3.33	0.75 - 8.00
T _{1/2} (hr)	18.3**	8.30 - 44.0
AUC (µg·min/mL)	4242	3200 - 6250
Bioavailability (%)	78.5	59.3 - 106
Vd _{ss} (L/kg)***	0.77	0.68 - 0.85
Cl _t (mL/min/kg)***	3.75	3.17 - 4.31

* harmonic mean
** mean value
*** following IV administration

C_{max} Maximum serum concentration
T_{max} Time at which C_{max} is observed
T_{1/2} Biological half-life
AUC Area under the curve
Vd_{ss} Volume of distribution at steady state
Cl_t Total body clearance

Florfenicol was detectable in the serum of most animals through 60 hours after intramuscular administration with a mean concentration of 0.19 µg/mL. The protein binding of florfenicol was 12.7%, 13.2%, and 18.3% at serum concentrations of 0.5, 3.0, and 18.0 µg/mL, respectively.

MICROBIOLOGY Florfenicol is a synthetic, broad-spectrum antibiotic active against many gram-negative and gram-positive bacteria isolated from domestic animals. It acts by binding to the 50S ribosomal subunit and inhibiting bacterial protein synthesis. Florfenicol is generally considered a bacteriostatic drug, but exhibits bactericidal activity against certain bacterial strains. *In vitro* and *in vivo* activity has been demonstrated against commonly isolated pathogens involved in bovine respiratory disease (BRD) including *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* (formerly *Haemophilus somnus*). Clinical studies confirm the efficacy of florfenicol against bovine respiratory disease as well as against commonly isolated bacterial pathogens in bovine interdigital phlegmon including *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*. The minimum inhibitory concentrations (MICs) of florfenicol for BRD organisms were determined using isolates obtained from natural infections from 1930 to 1993. The MICs for interdigital phlegmon organisms were determined using isolates obtained from natural infections from 1973 to 1997 (Table 2).

TABLE 2. MIC Values* of Florfenicol Against Bacterial Isolates From Natural Infection of Cattle

Organism	Isolate Numbers	MIC ₅₀ ** (µg/mL)	MIC ₉₀ ** (µg/mL)
<i>Mannheimia haemolytica</i>	398	0.50	1.00
<i>Pasteurella multocida</i>	350	0.50	0.50
<i>Histophilus somni</i> (<i>Haemophilus somnus</i>)	66	0.25	0.50
<i>Fusobacterium necrophorum</i>	33	0.25	0.25
<i>Bacteroides melaninogenicus</i>	20	0.25	0.25

* The correlation between the *in vitro* susceptibility data (MIC values) and clinical response has not been determined.
** The minimum inhibitory concentration for 50% and 90% of the isolates.

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*).

PRODUCT INFORMATION

RESIDUE WARNINGS: Animals intended for human consumption must not be slaughtered within 28 days of the last intramuscular treatment. Animals intended for human consumption must not be slaughtered within 38 days of subcutaneous treatment. Do not use in female dairy cattle 20 months of age or older. Use of florfenicol in this class of cattle may cause milk residues. A withdrawal period has not been established in preruminating calves. Do not use in calves to be processed for veal.

WARNINGS: NOT FOR HUMAN USE. KEEP OUT OF 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.

CAUTION Not for use in cattle of breeding age. The effects of florfenicol on bovine reproductive performance, pregnancy, and lactation have not been determined. Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck is likely to be more severe.


ADVERSE EFFECTS Inappetence, decreased water consumption, or diarrhea may occur transiently following treatment.

TOXICOLOGY A 10X safety study was conducted in feeder calves. Two intramuscular injections of 200 mg/kg were administered at a 48-hour interval. The calves were monitored for 14 days after the second dose. Marked anorexia, decreased water consumption, decreased body weight, and increased serum enzymes were observed following dose administration. These effects resolved by the end of the study. A 1X, 3X, and 5X (20, 60, and 100 mg/kg) safety study was conducted in feeder calves for 3X the duration of treatment (8 injections at 48-hour intervals). Slight decrease in feed and water consumption was observed in the 1X dose group. Decreased feed and water consumption, body weight, urine pH, and increased serum enzymes, were observed in the 3X and 5X dose groups. Depression, soft stool consistency, and dehydration were also observed in some animals (most frequently at the 3X and 5X dose levels), primarily near the end of dosing. A 43-day controlled study was conducted in healthy cattle to evaluate effects of NUFLOR Injectable Solution administered at the recommended dose on feed consumption. Although a transient decrease in feed consumption was observed, NUFLOR Injectable Solution administration had no long-term effect on body weight, rate of gain, or feed consumption.

DOSAGE AND ADMINISTRATION For treatment of bovine respiratory disease (BRD) and bovine interdigital phlegmon (foot rot): 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.**

NOTE: Intramuscular injection may result in local tissue reaction which persists beyond 28 days. This may result in trim loss of edible tissue at slaughter. Tissue reaction at injection sites other than the neck is likely to be more severe.

For control of respiratory disease in cattle at high-risk of developing BRD: 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.**

ANIMAL WEIGHT (lbs)	NUFLOR DOSAGE GUIDE		Recommended Injection Location
	IM NUFLOR DOSAGE 3.0 mL/100 lb Body Weight (mL)	SC NUFLOR DOSAGE 6.0 mL/100 lb Body Weight (mL)	
100	3.0	6.0	 Do not inject more than 10 mL per injection site.
200	6.0	12.0	
300	9.0	18.0	
400	12.0	24.0	
500	15.0	30.0	
600	18.0	36.0	
700	21.0	42.0	
800	24.0	48.0	
900	27.0	54.0	
1000	30.0	60.0	

Clinical improvement should be evident in most treated subjects within 24 hours of initiation of treatment. If a positive response is not noted within 72 hours of initiation of treatment, the diagnosis should be re-evaluated.

STORAGE CONDITIONS Store between 2°-30°C (36°-86°F). Refrigeration is not required. The solution is light yellow to straw colored. Color does not affect potency.

HOW SUPPLIED NUFLOR Injectable Solution is packaged in 100 mL (NDC 0061-1116-04), 250 mL (NDC 0061-1116-05), and 500 mL (NDC 0061-1116-06) glass sterile multiple-dose vials.

REFERENCE 1. Lobell RD, Varma KJ, et al. Pharmacokinetics of florfenicol following intravenous and intramuscular doses to cattle. *J Vet Pharmacol Therap.* 1994;17:253-258.

Made in Germany

Copyright © 1996, 2006, Schering-Plough Animal Health Corp., Summit, NJ 07901. All rights reserved. 24823148 Rev 2/07

WHEN DOES IT MAKE SENSE TO TREAT FOR BRD?

When bacterial populations are small?

**Or when they number
in the trillions?**

BACTERIAL POPULATIONS CAN DOUBLE EVERY 30 MINUTES

NUFLOR® ANTIBIOTIC ACTS FAST TO KEEP BACTERIA FROM MULTIPLYING.

In a 24-Hour Period, One Bacterium Can Grow to Trillions

The key to successful BRD treatment is quick action. That's why NUFLOR is so effective. If even one bacterial organism gets into the lungs, within 24 hours, there could be trillions causing lung tissue damage and producing toxins that spread throughout the body.

Successful BRD Treatment Starts Early with NUFLOR Antibiotic

You don't have to wait for NUFLOR to start working. Within 30 minutes, NUFLOR reaches minimum bactericidal concentration (MBC) and reaches peak concentrations in about an hour.

- NUFLOR begins *killing* bacteria within 30 minutes*
- NUFLOR reaches peak concentrations in about one hour

CAN YOU AFFORD TO WAIT FOR YOUR ANTIBIOTIC TO KICK IN?

Do not use in female dairy cattle 20 months of age or older, as use in lactating dairy cattle may cause milk residues. Not for use in cattle of breeding age. Do not use for calves to be processed for veal.

 Schering-Plough

Nuflor®
(FLORFENICOL)

**The One Cattleman
Count On**



*Exhibits bactericidal activity against some strains of Mannheimia haemolytica and Histophilus somni.
Copyright © 2007, Schering-Plough Animal Health Corporation. All rights reserved. Nuflor is a registered trademark of Schering-Plough Animal Health Corporation. SPAH-NFL-608