

NADA #141-206, Approved by FDA.

Nuflor®

(FLORFENICOL) An Antimicrobial 2.3% Concentrate Solution

For Oral Use in Swine Drinking Water Only

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

DESCRIPTION: Florfenicol (Oral Concentrate) is a synthetic broad-spectrum antibiotic. Each milliliter (mL) of Nuflor® 2.3% Concentrate Solution contains 23 mg florfenicol.

INDICATIONS: Nuflor 2.3% Concentrate Solution is indicated for the treatment of swine respiratory disease associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Salmonella choleraesuis*, and *Streptococcus suis* Type 2 in swine.

DOSAGE AND ADMINISTRATION:

For Proportioner: To produce drinking water with a final concentration of 400 mg/gallon (100 ppm): Fill the bottle of Nuflor Concentrate Solution with water to the fill line. Add the contents of the bottle to the mixing tank. Mix thoroughly. Confirm that the proportioner is set to deliver 1:128 (0.8%). Turn on the proportioner. Verify that the drinkers are operational.

For Bulk Tank: To produce drinking water with a final concentration of 400 mg/gallon (100 ppm): Add the Nuflor Concentrate Solution to the drinking water in the bulk tank. Use one bottle of Nuflor Concentrate Solution for every 128 gallons of water.

The medicated water should be administered as the only source of drinking water for 5 consecutive days. Medication should be initiated promptly when swine respiratory disease is diagnosed.

PRECAUTIONS: Do not use this product at any other proportioner setting. This will result in precipitation of product. This product is not recommended for use in automatic water proportioners if water hardness is greater than 275 ppm. Water proportioners should be tested for accuracy before use. Do not use or store this product in galvanized metal watering systems or containers. Do not operate chlorinators while administering medication.

RESIDUE WARNINGS: Swine intended for human consumption must not be slaughtered within 16 days of the last treatment. Use of this product in a manner other than indicated or with dosages in excess of those included on this label may result in illegal drug residues in edible tissues.

WARNINGS: NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN. This product contains material that can be irritating to skin and eyes. Avoid direct contact with skin, eyes, and clothes. 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. The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information.

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

For adverse effects reporting, call 1-800-219-9286.

PRECAUTION: The effects of Nuflor® 2.3% Concentrate Solution on the reproductive function of treated swine have not been determined. Do not use in swine intended for breeding.

ADVERSE REACTIONS: Perianal inflammation may occur transiently following treatment.

CLINICAL PHARMACOLOGY: Florfenicol is a bacteriostatic agent whose antimicrobial activity is linked to time above MIC.

The pharmacokinetic disposition of Nuflor® 2.3% Concentrate Solution was evaluated in swine following oral gavage dosing (15 mg/kg), intravenous (IV) dosing (15 mg/kg), and during a 5-day course of *ad libitum* administration in drinking water (100 ppm) (Table 1). Despite the rapid elimination seen after IV injection or oral gavage dosing, when administered in medicated drinking water, florfenicol concentrations in the serum of most swine were maintained well above 1.0 mcg/mL for the majority of the 5-day dosing interval. These results are consistent with product effectiveness when administered in drinking water concentrations of 100 ppm over a 5-day dosing period.

Although the extent of oral drug absorption (F) tended to be variable (24% to 97% following a single oral gavage dose), florfenicol was rapidly absorbed. Its terminal elimination half-life (T_{1/2}) was also rapid, ranging between 2 to 3 hours. The average systemic clearance (CL_s) following IV administration was 5.6 mL/kg/min. Since the florfenicol steady state volume of distribution (V_{DSS}) closely approximates that of total body water, peripheral tissue concentrations are expected to be similar to those concentrations observed in serum.

Table 1. Pharmacokinetic Parameter Values of Florfenicol following IV or Gavage Dosing

Parameter	Mean Value (%CV)
V _{DSS} ^a (L/kg)	0.95 (6)
CL _s ^a (mL/kg/min)	5.57 (11)
T _{1/2} ^a (hrs)	2.2 (14)
F ^b (%)	24-97

^aparameter estimate based on intravenous data

^bparameter range based upon a single oral gavage dose

MICROBIOLOGY: Florfenicol is a synthetic broad-spectrum antibiotic active against many gram-negative and gram-positive bacteria isolated from domestic animals. It acts by inhibiting bacterial protein synthesis. *In vivo* and *in vitro* activity has been demonstrated against commonly isolated pathogens involved in swine respiratory disease including *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Salmonella choleraesuis*, and *Streptococcus suis* Type 2.

The minimum inhibitory concentration (MIC) of florfenicol was determined for isolates obtained from natural respiratory infections of swine from 1990-2001 (Table 2). Susceptibility testing followed the methods of the National Committee of Clinical Laboratory Standards. Reference strains included *Escherichia coli* ATCC 25922 with a QC range of 2-8 mcg/mL and *Actinobacillus pleuropneumoniae* ATCC 27090 with a QC range of 0.25-1 mcg/mL.

Table 2. MIC Values of Florfenicol Against Bacterial Isolates from Swine

Organism	Isolate Numbers	MIC ₉₀ ^a (mcg/mL)	MIC Range (mcg/mL)
<i>Actinobacillus pleuropneumoniae</i>	360	0.50	≤0.125-2.0
<i>Pasteurella multocida</i>	335	0.50	≤0.125-2.0
<i>Salmonella choleraesuis</i>	46	4.0	2.0-4.0
<i>Streptococcus suis</i> Type 2	203	2.0	0.5-2.0

^aThe minimum inhibitory concentration for 90% of the isolates

ANIMAL SAFETY: A target animal safety study was conducted to evaluate the tolerance and effects of Nuflor® 2.3% Concentrate Solution (florfenicol) when orally administered to swine via the drinking water at a rate of 400, 1200, and 2000 mg/gal (1x, 3x, or 5x the clinical dose) for 15 to 16 consecutive days (3x the clinical duration), and at 4000 mg/gal (10x clinical dose) for 5 to 6 consecutive days (1x the clinical duration). Transient treatment-related constipation and anal swelling were seen in the 3x, 5x, and 10x treatment groups. The constipation in these groups was attributed in part to decreased water consumption during the medication period. There was a decrease in weight gains for the 3x, 5x, and 10x treatment groups compared with the nonmedicated control group. Transient treatment-related decreases in feed consumption were seen in the 3x, 5x, and 10x treatment groups compared with the nonmedicated control group. Transient treatment-related decreases in water consumption were noted in all test article-treated groups (1x, 3x, 5x, and 10x) compared with the nonmedicated control group.

The results show that Nuflor 2.3% Concentrate Solution can be safely administered to swine according to the recommended clinical regimen of 400 mg/gal in the drinking water for 5 consecutive days.

STORAGE CONDITIONS: Store between 2°-25°C (36°-77°F).

HOW SUPPLIED: Nuflor 2.3% Concentrate Solution is supplied in one gallon plastic bottles with a 2.2 liter fill.

Made in Ireland.