Norfenicol®
(florfenicol)

- Shorter Sub-Q Withdrawal Time Than Nuflor®
- Less Viscous and More Syringeable Than Nuflor*
- New Plastic Bottles Eliminate Breakage and Product Loss
- FDA-Approved for Sub-Q Use in Cattle at High-Risk of BRD
- Broad Spectrum Treatment and Control Against BRD
- Unique Formulation

***Data on file**

Observe label directions and withdrawal times. Federal law restricts this drug to use by or on the order of a licensed veterinarian. For use in beef and non-lactating dairy cattle only. Not approved for use in female dairy cattle 20 months of age or older, including dry dairy cows. Animals intended for human consumption must not be slaughtered within 28 days of the last intramuscular treatment or within 33 days of subcutaneous treatment. Do not use in calves to be processed for veal. Intramuscular injection may result in local tissue reaction which may result in trim loss at slaughter. See product labeling for full product information, including adverse reactions.

www.norbrookinc.com

FOR VETERINARY USE ONLY

Norbrook®

Bovine Respiratory Disease (BRD) is the most common and costly disease affecting the beef cattle industry. BRD (also referred to as Shipping Fever) is associated with infections of the lungs causing pneumonia. This condition is often seen in stressed and high risk cattle. BRD is often reported as the main cause of morbidity (sickness) and mortality (deaths) in feedlots.

BRD is a multi-factorial disease that involves an interaction between several factors, including:

- **Environmental factors** such as transport, co-mingling, crowding, weather fluctuations, etc.
- **Infectious agents including:**
  - Bacteria
  - Viruses
  - Parasites

Q. What is Norfenicol® Injectable Solution?

A. **Norfenicol Injectable Solution** is a broad-spectrum, fast-acting injectable antibiotic containing florfenicol. **Norfenicol** contains the same active ingredient and is bioequivalent to Nuflor® (florfenicol).

Q. What is Norfenicol® indicated for?

A. **Norfenicol** is indicated for **treatment** of bovine respiratory disease (BRD) associated with *M. haemolytica*, *P. multocida*, and *H. somni* – the three primary bacterial pathogens associated with BRD. It is also indicated for the **control** of respiratory disease in cattle at high risk of developing BRD associated with *M. haemolytica*, *P. multocida*, and *H. somni*.

Norfenicol is also indicated for the **treatment** of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with *F. necrophorum* and *B. melaninogenicus*.

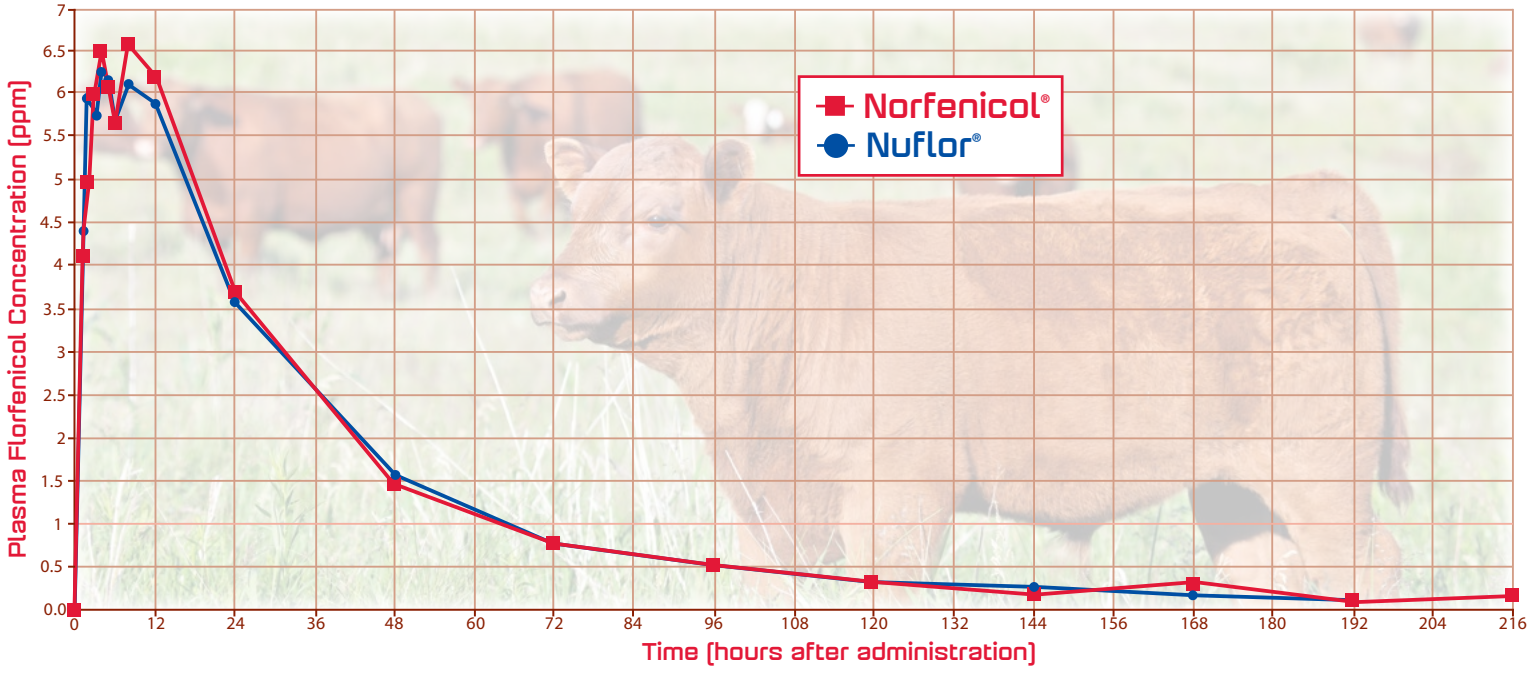
Q. What makes Norfenicol® effective when treating BRD?

A. **Norfenicol** is a broad-spectrum, highly effective antibiotic that inhibits bacterial protein synthesis. **Norfenicol** has both bacteriostatic and bactericidal activity against the major pathogens of BRD. In addition, it has a high volume of distribution allowing it to get to the site of infection for effective treatment and control of BRD.

Q. How quickly is Norfenicol® absorbed and distributed to the site of infection?

A. **Norfenicol** reaches therapeutic levels quickly – usually within 30 minutes after administration. Florfenicol remained therapeutically active in the blood through at least 60 hours (2.5 + days). The fast absorption delivers rapid onset of action.

Mean Plasma Concentrations of Florfenicol (ppm) in Cattle Following a Single SQ Administration at an Approximate Dose Rate of 40 mg florenicol/kg Body Weight



Q. What are the product benefits of Norfenicol®?

A. **Norfenicol** is an excellent first-choice, broad-spectrum antibiotic for the **treatment** and **control** of BRD and **treatment** of footrot. The major benefits of **Norfenicol** include:

- **Shorter Sub-Q withdrawal period vs. Nuflor** – For one-dose Sub-Q **Norfenicol**, the withdrawal period is 33 days (vs. Nuflor at 38 days) prior to slaughter. For two-dose IM **Norfenicol**, the withdrawal period is 28 days prior to slaughter.
- **Enhanced Product Characteristics** – Tests show that **Norfenicol** is less viscous and more syringeable than Nuflor, allowing for easier use and administration.
- **New Plastic Bottles** – **Norfenicol** is the only injectable cattle antibiotic sold in the U.S. that is packaged in unbreakable plastic bottles. No more "protective sleeves" to deal with and no more expensive product losses due to breakage.
- **Flexible Sub-Q Dosing to fit your management practices**
  - **High Risk Cattle** – **Norfenicol** can be used in high-risk cattle entering a feedyard. A single 6-mL/100 lbs. Sub-Q dose on arrival quickly and effectively helps reduce morbidity and mortality rates.
  - **Hospital Treatment** – **Norfenicol**, either at one dose Sub-Q at 6 mL/100 lbs. **OR** two doses Intramuscular (IM) at 3 mL/100 lbs., two days apart, quickly provides effective relief from BRD.

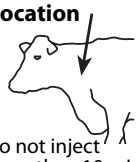
Florfenicol Comparison

Comparisons	Norfenicol®	Nuflor®
Pathogens	M. haemolytica	M. haemolytica
	P. multocida	P. multocida
	H. somni	H. somni
	Fusobacterium Bacteroides	Fusobacterium Bacteroides
Indications	Treat BRD	Treat BRD
	Control BRD	Control BRD
	Treat Footrot	Treat Footrot
Withdrawal	33 Days (SQ)	38 Days (SQ)
	28 Days (IM)	28 Days (IM)
Dose (SQ)	6 mL/cwt	6 mL/cwt
Dose (IM)	3 mL/cwt repeat 48 hrs later	3 mL/cwt repeat 48 hrs later
mLs Per Injection Site	10 mL	10 mL
Florfenicol Concentration	300 mg/mL	300 mg/mL
Bottle Composition	Plastic	Glass

Norfenicol Injectable Solution Dosage Guide

Animal Weight (lbs)	IM Dosage 3.0 mL/100 lb Body Weight (mL)	SC Dosage 6.0 mL/100 lb Body Weight (mL)
100	3.0	6.0
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

Recommended Injection Location



Do not inject more than 10 mL per injection site

- **Fast Therapy** – Reaches therapeutic levels within 30 minutes after injection that promotes faster recovery from BRD and footrot.

Q. Can Norfenicol® be used in lactating dairy cows?

A. Do not use in female dairy cattle 20 months of age or older or in calves to be processed for veal.

Q. How is Norfenicol® supplied?

A. **Norfenicol Injectable Solution** is packaged in 100 mL, 250 mL, and 500 mL **plastic** bottles.

Norfenicol® (florfenicol)

ANADA 200-591, Approved by FDA

PRODUCT INFORMATION

Norfenicol®

(florfenicol)

Injectable Solution

300 mg/mL

For intramuscular and subcutaneous use in beef and non-lactating dairy cattle only.

Not for use in female dairy cattle 20 months of age or older or in calves to be processed for veal.

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

DESCRIPTION: Norfenicol® Injectable Solution is a solution of the synthetic antibiotic florfenicol. Each milliliter of sterile Norfenicol Injectable Solution contains 300 mg of florfenicol, 250 mg 2-pyrrolidone, and glycerol formal qs.

INDICATIONS: Norfenicol Injectable Solution is indicated for treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida*, and *Histophilus somni*, 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*.

DOSAGE AND ADMINISTRATION: For treatment of bovine respiratory disease (BRD) and bovine interdigital phlegmon (foot rot): Norfenicol 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, Norfenicol Injectable Solution can be administered by a single subcutaneous (SC) 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.

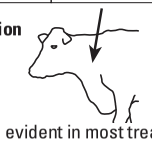
For control of respiratory disease in cattle at high-risk of developing BRD: Norfenicol Injectable Solution should be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (6 mL/100lbs). Do not administer more than 10 mL at each site. The injection should be given only in the neck.

NORFENICOL INJECTABLE SOLUTION DOSAGE GUIDE

ANIMAL WEIGHT (lbs)	IM DOSAGE 3.0 mL/100 lb Body Weight (mL)	SC DOSAGE 6.0 mL/100 lb Body Weight (mL)
100	3.0	6.0
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

Recommended Injection Location

Do not inject more than 10 mL per injection site.



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.

CONTRAINDICATIONS: Do not use in animals that have shown hypersensitivity to florfenicol.

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 1-866-591-5777.

PRECAUTIONS: Not for use in animals intended for breeding purposes. The effects of florfenicol on bovine reproductive performance, pregnancy, and lactation have not been determined. Toxicity studies in dogs, rats, and mice have associated the use of florfenicol with testicular degeneration and atrophy. 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.

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 33 days of subcutaneous treatment. This product is not approved for use in female dairy cattle 20 months of age or older, including dry dairy cows. Use in these cattle may cause drug residues in milk and/or in calves born to these cows. A withdrawal period has not been established in pre-ruminating calves. Do not use in calves to be processed for veal.

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

CLINICAL PHARMACOLOGY: The pharmacokinetic disposition of florfenicol injectable solution was evaluated in feeder calves following single intramuscular (IM) administration at the recommended dose of 20 mg/kg body weight. Florfenicol injectable solution was also administered intravenously (IV) to the same cattle in order to calculate the volume of distribution, clearance, and percent bioavailability[1] (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
$T_{½}$ (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
$T_{½}$ Biological half-life
AUC Area under the curve
Vd_{SS} Volume of distribution at steady state
Cl_t Total body clearance

Florfenicol was detectible 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 16.0 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 species. *In vitro* studies demonstrate that florfenicol is active against the bovine respiratory disease (BRD) pathogens *Mannheimia haemolytica, Pasteurella multocida*, and *Histophilus somni*, and that florfenicol exhibits bactericidal activity against strains of *M. haemolytica* and *H. somni*. Clinical studies confirm the efficacy of florfenicol against BRD 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 1990 to 1993. The MICs for interdigital phlegmon organisms were determined using isolates obtained from natural infections from 1973 to 1997 (Table 2).

000000101

March 2015

TABLE 2. Florfenicol Minimum Inhibitory Concentration (MIC) Values*of Indicated Pathogens Isolated from Natural Infections of Cattle.

Indicated Pathogens	Year of Isolation	Number of isolates	MIC_{50}** (µg/mL)	MIC_{90}** (µg/mL)
Mannheimia haemolytica	1990 to 1993	398	0.5	1
Pasteurella multocida	1990 to 1993	350	0.5	0.5
Histophilus somni	1990 to 1993	66	0.25	0.5
Fusobacterium necrophorum	1973 to 1997	33	0.25	0.25
Bacteroides melaninogenicus	1973 to 1997	20	0.25	0.25

* The correlation between the *in vitro* susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% to 90% of the most suceptible isolates, respectively.

ANIMAL SAFETY: 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 (6 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 florfenicol injectable solution administered at the recommended dose on feed consumption. Although a transient decrease in feed consumption was observed, florfenicol injectable solution administration had no long-term effect on body weight, rate of gain, or feed consumption.

STORAGE INFORMATION: Store at or below 77°F (25°C). Refrigeration is not required. Excursions permitted up to 86°F (30°C). Brief exposure to temperature up to 104°F (40°C) may be tolerated provided the mean kinetic temperature does not exceed 77°F (25°C); however, such exposure should be minimized. The solution is light yellow to straw colored. Color does not affect potency.
Use within 28 days of first vial puncture.

HOW SUPPLIED: Norfenicol Injectable Solution is packaged in 100 mL, 250 mL, and 500 mL 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.

Restriced Drug – California. Use Only as Directed.
Made in the UK.
Manufactured by: Norbrook Laboratories Limited, Newry, BT35 6PU, Co. Down, Northern Ireland.

Norbrook®

0816-591-101B