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).

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 Laboratories Ltd - Norfenicol
Res : 60686

SECTION 1: IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY/UNDERTAKING

1.1 Product identifier: Norbrook Laboratories Ltd - Norfenicol
Res : 60686

1.2 Relevant identified uses of the substance or mixture and uses advised against:

Relevant uses: Veterinary Pharmaceutical Product

Uses advised against: All uses not specified in this section or in section 7.3

1.3 Details of the supplier of the safety data sheet:

Norbrook Laboratories Ltd
Carnbane Industrial Estate
BT35 6QQ Newry - Northern Ireland
Phone.: +44 (0)28 3026 4435 -
Fax: +44 (0)28 3026 5060
http://www.norbrook.com

1.4 Emergency telephone number: +44 (0)28 3026 4435

SECTION 2: HAZARDS IDENTIFICATION

2.1 Classification of the substance or mixture:

CLP Regulation (EC) nº 1272/2008:

Classification of this product has been carried out in accordance with CLP Regulation (EC) nº 1272/2008.

Eye Irrit. 2: Eye irritation, Category 2, H319
Skin Irrit. 2: Skin irritation, Category 2, H315

2.2 Label elements:

CLP Regulation (EC) nº 1272/2008:

Warning

Hazard statements:

Eye Irrit. 2: H319 - Causes serious eye irritation
Skin Irrit. 2: H315 - Causes skin irritation

Precautionary statements:

P101: If medical advice is needed, have product container or label at hand
P102: Keep out of reach of children
P264: Wash thoroughly after use
P280: Wear protective gloves/protective clothing/eye protection/face protection
P302+P352: IF ON SKIN: Wash with plenty of water
P305+P351+P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing
P337+P313: If eye irritation persists: Get medical advice/attention
P501: Dispose of contents and / or their container according to the separated collection system used in your municipality

2.3 Other hazards:

Non-applicable

SECTION 3: COMPOSITION/INFORMATION ON INGREDIENTS

3.1 Substance:

Non-applicable

3.2 Mixture:

Chemical description: Injection Solution

Components:

In accordance with Annex II of Regulation (EC) nº1907/2006 (point 3), the product contains:

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SECTION 3: COMPOSITION/INFORMATION ON INGREDIENTS (continue)

Identification	Chemical name/Classification		Concentration
CAS: 616-45-5 EC: 210-483-1 Index: Non-applicable REACH: 01-2119475471-37-XXXX	**2-pyrrolidone**	Self-classified	**25 - <50 %**
	Regulation 1272/2008	Eye Irrit. 2: H319; Skin Irrit. 2: H315 - Warning	
CAS: 5464-28-8 EC: 226-758-4 Index: Non-applicable REACH: Non-applicable	**1,3-dioxolan-4-ylmethanol**	Self-classified	**1 - <2.5 %**
	Regulation 1272/2008	Eye Irrit. 2: H319 - Warning	

To obtain more information on the risk of the substances consult sections 8, 11, 12, 15 and 16.

SECTION 4: FIRST AID MEASURES

4.1 Description of first aid measures:

The symptoms resulting from intoxication can appear after exposure, therefore, in case of doubt, seek medical attention for direct exposure to the chemical product or persistent discomfort, showing the SDS of this product.

By inhalation:

This product does not contain substances classified as hazardous for inhalation, however, in case of symptoms of intoxication remove the person affected from the exposure area and provide with fresh air. Seek medical attention if the symptoms get worse or persist.

By skin contact:

Remove contaminated clothing and footwear, rinse skin or shower the person affected if appropriate with plenty of cold water and neutral soap. In serious cases see a doctor. If the product causes burns or freezing, clothing should not be removed as this could worsen the injury caused if it is stuck to the skin. If blisters form on the skin, these should never be burst as this will increase the risk of infection.

By eye contact:

Rinse eyes thoroughly with lukewarm water for at least 15 minutes. Do not allow the person affected to rub or close their eyes. If the injured person uses contact lenses, these should be removed unless they are stuck to the eyes, as this could cause further damage. In all cases, after cleaning, a doctor should be consulted as quickly as possible with the SDS of the product.

By ingestion/aspiration:

Do not induce vomiting, but if it does happen keep the head down to avoid aspiration. Keep the person affected at rest. Rinse out the mouth and throat, as they may have been affected during ingestion.

4.2 Most important symptoms and effects, both acute and delayed:

Acute and delayed effects are indicated in sections 2 and 11.

4.3 Indication of any immediate medical attention and special treatment needed:

Non-applicable

SECTION 5: FIREFIGHTING MEASURES

5.1 Extinguishing media:

Product is non-flammable under normal conditions of storage, manipulation and use. In the case of inflammation as a result of improper manipulation, storage or use preferably use polyvalent powder extinguishers (ABC powder), in accordance with the Regulation on fire protection systems. IT IS NOT RECOMMENDED to use tap water as an extinguishing agent.

5.2 Special hazards arising from the substance or mixture:

As a result of combustion or thermal decomposition reactive sub-products are created that can become highly toxic and, consequently, can present a serious health risk.

5.3 Advice for firefighters:

Depending on the magnitude of the fire it may be necessary to use full protective clothing and individual respiratory equipment. Minimum emergency facilities and equipment should be available (fire blankets, portable first aid kit,...) in accordance with Directive 89/654/EC.

Additional provisions:

Act in accordance with the Internal Emergency Plan and the Information Sheets on actions to take after an accident or other emergencies. Destroy any source of ignition. In case of fire, refrigerate the storage containers and tanks for products susceptible to inflammation, explosion or BLEVE as a result of high temperatures. Avoid spillage of the products used to extinguish the fire into an aqueous medium.

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SECTION 6: ACCIDENTAL RELEASE MEASURES

6.1 Personal precautions, protective equipment and emergency procedures:

Isolate leaks provided that there is no additional risk for the people performing this task. Personal protection equipment must be used against potential contact with the spilt product (See section 8). Evacuate the area and keep out those who do not have protection.

6.2 Environmental precautions:

This product is not classified as hazardous to the environment. Keep product away from drains, surface and underground water.

6.3 Methods and material for containment and cleaning up:

It is recommended:

Absorb the spillage using sand or inert absorbent and move it to a safe place. Do not absorb in sawdust or other combustible absorbents. For any concern related to disposal consult section 13.

6.4 Reference to other sections:

See sections 8 and 13.

SECTION 7: HANDLING AND STORAGE

7.1 Precautions for safe handling:

A.- Precautions for safe manipulation

Comply with the current legislation concerning the prevention of industrial risks. Keep containers hermetically sealed. Control spills and residues, destroying them with safe methods (section 6). Avoid leakages from the container. Maintain order and cleanliness where dangerous products are used.

B.- Technical recommendations for the prevention of fires and explosions

Product is non-flammable under normal conditions of storage, manipulation and use. It is recommended to transfer at slow speeds to avoid the generation of electrostatic charges that can affect flammable products. Consult section 10 for information on conditions and materials that should be avoided.

C.- Technical recommendations to prevent ergonomic and toxicological risks

Do not eat or drink during the process, washing hands afterwards with suitable cleaning products.

D.- Technical recommendations to prevent environmental risks

It is recommended to have absorbent material available at close proximity to the product (See subsection 6.3)

7.2 Conditions for safe storage, including any incompatibilities:

A.- Technical measures for storage

Maximun Temp.: 25 ºC

B.- General conditions for storage

Avoid sources of heat, radiation, static electricity and contact with food. For additional information see subsection 10.5

7.3 Specific end use(s):

Cattle:
Treatment of respiratory tract infections in clinically diseased cattle due to Mannheima haemolytica, Pasteurella multocida and Histophilus somni, suscepticle to Florfenicol.

Swine:
Treatment of acute outbreaks of respiratory disease caused by strains of Actinobacillus pleuropneumoniae and Pasteurella multocida, susceptible to Florfenicol.

SECTION 8: EXPOSURE CONTROLS/PERSONAL PROTECTION

8.1 Control parameters:

Substances whose occupational exposure limits have to be monitored in the work environment

There are no environmental limits for the substances contained in the product

DNEL (Workers):

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SECTION 8: EXPOSURE CONTROLS/PERSONAL PROTECTION (continue)

Identification		Short exposure		Long exposure	
		Systemic	Local	Systemic	Local
2-pyrrolidone	Oral	Non-applicable	Non-applicable	Non-applicable	Non-applicable
CAS: 616-45-5	Dermal	277 mg/kg	Non-applicable	10 mg/kg	Non-applicable
EC: 210-483-1	Inhalation	Non-applicable	Non-applicable	57.8 mg/m³	Non-applicable

DNEL (General population):

Identification		Short exposure		Long exposure	
		Systemic	Local	Systemic	Local
2-pyrrolidone	Oral	33.3 mg/kg	Non-applicable	5.2 mg/kg	Non-applicable
CAS: 616-45-5	Dermal	167 mg/kg	Non-applicable	6 mg/kg	Non-applicable
EC: 210-483-1	Inhalation	Non-applicable	Non-applicable	17.1 mg/m³	Non-applicable

PNEC:

Identification				
2-pyrrolidone	STP	10 mg/L	Fresh water	0.5 mg/L
CAS: 616-45-5	Soil	0.0612 mg/kg	Marine water	0.05 mg/L
EC: 210-483-1	Intermittent	0.5 mg/L	Sediment (Fresh water)	0.4205 mg/kg
	Oral	Non-applicable	Sediment (Marine water)	Non-applicable

8.2 Exposure controls:

A.- General security and hygiene measures in the work place

As a preventative measure it is recommended to use basic Personal Protection Equipment, with the corresponding <<CE marking>> in accordance with Directive 89/686/EC. For more information on Personal Protection Equipment (storage, use, cleaning, maintenance, class of protection,…) consult the information leaflet provided by the manufacturer. For more information see subsection 7.1.
All information contained herein is a recommendation which needs some specification from the labour risk prevention services as it is not known whether the company has additional measures at its disposal.

B.- Respiratory protection

The use of protection equipment will be necessary if a mist forms or if the professional exposure limits are exceeded.

C.- Specific protection for the hands

Pictogram	PPE	Labelling	CEN Standard	Remarks
 Mandatory hand protection	Chemical protective gloves	CE CAT I	EN 420:2003+A1:2009	Replace the gloves at any sign of deterioration.

D.- Ocular and facial protection

Pictogram	PPE	Labelling	CEN Standard	Remarks
 Mandatory face protection	Panoramic glasses against liquid splash	CE CAT II	EN 166:2001 EN 172:1994/A1:2000 EN 172:1994/A2:2001 EN ISO 4007:2012	Clean daily and disinfect periodically according to the manufacturer´s instructions. Use if there is a risk of splashing.

E.- Bodily protection

Pictogram	PPE	Labelling	CEN Standard	Remarks
	Work clothing	CE CAT I	EN ISO 13688:2013	For professional use only.
	Anti-slip work shoes	CE CAT II	EN ISO 20347:2012 EN ISO 20344:2011	None

F.- Additional emergency measures

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SECTION 8: EXPOSURE CONTROLS/PERSONAL PROTECTION (continue)

Emergency measure	Standards	Emergency measure	Standards
 Emergency shower	ANSI Z358-1 ISO 3864-1:2002	 Eyewash stations	DIN 12 899 ISO 3864-1:2002

Environmental exposure controls:

In accordance with the community legislation for the protection of the environment it is recommended to avoid environmental spillage of both the product and its container. For additional information see subsection 7.1.D

Volatile organic compounds:

With regard to Directive 2010/75/EU, this product has the following characteristics:

V.O.C. (Supply):	45 % weight
V.O.C. density at 20 ºC:	519.69 kg/m³ (519.69 g/L)
Average carbon number:	4
Average molecular weight:	104.1 g/mol

SECTION 9: PHYSICAL AND CHEMICAL PROPERTIES

9.1 Information on basic physical and chemical properties:

For complete information see the product datasheet.

Appearance:

Physical state at 20 ºC:	Liquid
Appearance:	Undefined
Color:	Yellowish
Odor:	Undefined

Volatility:

Boiling point at atmospheric pressure:	193 ºC
Vapour pressure at 20 ºC:	39 Pa
Vapour pressure at 50 ºC:	353 Pa (0 kPa)
Evaporation rate at 20 ºC:	Non-applicable *

Product description:

Density at 20 ºC:	1155 kg/m³
Relative density at 20 ºC:	1.155
Dynamic viscosity at 20 ºC:	Non-applicable *
Kinematic viscosity at 20 ºC:	Non-applicable *
Kinematic viscosity at 40 ºC:	Non-applicable *
Concentration:	Non-applicable *
pH:	Non-applicable *
Vapour density at 20 ºC:	Non-applicable *
Partition coefficient n-octanol/water 20 ºC:	Non-applicable *
Solubility in water at 20 ºC:	Non-applicable *
Solubility properties:	Non-applicable *
Decomposition temperature:	Non-applicable *
Melting point/freezing point:	Non-applicable *

Flammability:

Flash Point:	Non Flammable (>60 ºC)
Autoignition temperature:	Non-applicable *

*Not relevant due to the nature of the product, not providing information property of its hazards.

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SECTION 9: PHYSICAL AND CHEMICAL PROPERTIES (continue)

Lower flammability limit:	Non-applicable *
Upper flammability limit:	Non-applicable *

9.2 Other information:

Surface tension at 20 ºC:	Non-applicable *
Refraction index:	Non-applicable *

*Not relevant due to the nature of the product, not providing information property of its hazards.

SECTION 10: STABILITY AND REACTIVITY

10.1 Reactivity:

No hazardous reactions are expected if the following technical instructions storage of chemicals. See section 7.

10.2 Chemical stability:

Chemically stable under the conditions of storage, handling and use.

10.3 Possibility of hazardous reactions:

Under the specified conditions, hazardous reactions that lead to excessive temperatures or pressure are not expected.

10.4 Conditions to avoid:

Applicable for handling and storage at room temperature:

Shock and friction	Contact with air	Increase in temperature	Sunlight	Humidity
Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

10.5 Incompatible materials:

Acids	Water	Combustive materials	Combustible materials	Others
Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

10.6 Hazardous decomposition products:

See subsection 10.3, 10.4 and 10.5 to find out the specific decomposition products. Depending on the decomposition conditions, complex mixtures of chemical substances can be released: carbon dioxide (CO2), carbon monoxide and other organic compounds.

SECTION 11: TOXICOLOGICAL INFORMATION

11.1 Information on toxicological effects:

The experimental information related to the toxicological properties of the product itself is not available

Dangerous health implications:

In case of exposure that is repetitive, prolonged or at concentrations higher than recommended by the occupational exposure limits, it may result in adverse effects on health depending on the means of exposure:

A.- Ingestion:

- Acute toxicity: Based on available data, the classification criteria are not met, as it does not contain substances classified as dangerous for consumption. For more information see section 3.
- Corrosivity/Irritability: The consumption of a considerable dose can cause irritation in the throat, abdominal pain, nausea and vomiting.

B- Inhalation:

- Acute toxicity: Based on available data, the classification criteria are not met, as it does not contain substances classified as dangerous for inhalation. For more information see section 3.
- Corrosivity/Irritability: Based on available data, the classification criteria are not met, as it does not contain substances classified as dangerous for this effect. For more information see section 3.

C- Contact with the skin and the eyes:

- Contact with the skin: Produces skin inflammation.
- Contact with the eyes: Produces eye damage after contact.

D- CMR effects (carcinogenicity, mutagenicity and toxicity to reproduction):

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SECTION 11: TOXICOLOGICAL INFORMATION (continue)

- Carcinogenicity: Based on available data, the classification criteria are not met, as it does not contain substances classified as dangerous for the effects mentioned. For more information see section 3.
- Mutagenicity: Based on available data, the classification criteria are not met, as it does not contain substances classified as dangerous for this effect. For more information see section 3.
- Reproductive toxicity: Based on available data, the classification criteria are not met, as it does not contain substances classified as dangerous for this effect. For more information see section 3.

E- Sensitizing effects:

- Respiratory: Based on available data, the classification criteria are not met, as it does not contain substances classified as dangerous with sensibilizising effects. For more information see section 3.
- Cutaneous: Based on available data, the classification criteria are not met, as it does not contain substances classified as dangerous for this effect. For more information see section 3.

F- Specific target organ toxicity (STOT)-time exposure:

Based on available data, the classification criteria are not met, as it does not contain substances classified as dangerous for this effect. For more information see section 3.

G- Specific target organ toxicity (STOT)-repeated exposure:

- Specific target organ toxicity (STOT)-repeated exposure: Based on available data, the classification criteria are not met, as it does not contain substances classified as dangerous for this effect. For more information see section 3.
- Skin: Based on available data, the classification criteria are not met, as it does not contain substances classified as dangerous for this effect. For more information see section 3.

H- Aspiration hazard:

Based on available data, the classification criteria are not met, as it does not contain substances classified as dangerous for this effect. For more information see section 3.

Other information:

Non-applicable

Specific toxicology information on the substances:

Identification	Acute toxicity		Genus
2-pyrrolidone	LD50 oral	6500 mg/kg	Rat
CAS: 616-45-5	LD50 dermal	Non-applicable	
EC: 210-483-1	LC50 inhalation	Non-applicable	

SECTION 12: ECOLOGICAL INFORMATION

The experimental information related to the eco-toxicological properties of the product itself is not available

12.1 Toxicity:

Not available

12.2 Persistence and degradability:

Not available

12.3 Bioaccumulative potential:

Identification	Bioaccumulation potential	
2-pyrrolidone	BCF	3
CAS: 616-45-5	Pow Log	-0.85
EC: 210-483-1	Potential	Low

12.4 Mobility in soil:

Identification	Absorption/desorption		Volatility	
2-pyrrolidone	Koc	17	Henry	1.074E-4 Pa·m³/mol
CAS: 616-45-5	Conclusion	Very High	Dry soil	No
EC: 210-483-1	Surface tension	45760 N/m (25 ºC)	Moist soil	No

12.5 Results of PBT and vPvB assessment:

Non-applicable

12.6 Other adverse effects:

Not described

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SECTION 13: DISPOSAL CONSIDERATIONS

13.1 Waste treatment methods:

Code	Description	Waste class (Regulation (EU) No 1357/2014)
16 03 05*	Organic wastes containing dangerous substances	Dangerous

Type of waste (Regulation (EU) No 1357/2014):

HP4 Irritant — skin irritation and eye damage

Waste management (disposal and evaluation):

Consult the authorized waste service manager on the assessment and disposal operations in accordance with Annex 1 and Annex 2 (Directive 2008/98/EC). As under 15 01 (2014/955/EC) of the code and in case the container has been in direct contact with the product, it will be processed the same way as the actual product. Otherwise, it will be processed as non-dangerous residue. We do not recommended disposal down the drain. See paragraph 6.2.

Regulations related to waste management:

In accordance with Annex II of Regulation (EC) nº1907/2006 (REACH) the community or state provisions related to waste management are stated

Community legislation: Directive 2008/98/EC, 2014/955/EU, Regulation (EU) No 1357/2014

SECTION 14: TRANSPORT INFORMATION

This product is not regulated for transport (ADR/RID,IMDG,IATA)

SECTION 15: REGULATORY INFORMATION

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture:

Candidate substances for authorisation under the Regulation (EC) 1907/2006 (REACH): Non-applicable

Substances included in Annex XIV of REACH ("Authorisation List") and sunset date: Non-applicable

Regulation (EC) 1005/2009, about substances that deplete the ozone layer: Non-applicable

Active substances for which a decision of non-inclusion onto Annex I (Regulation (EU) No 528/2012): Non-applicable

REGULATION (EU) No 649/2012, in relation to the import and export of hazardous chemical products: Non-applicable

Limitations to commercialisation and the use of certain dangerous substances and mixtures (Annex XVII, REACH):

Non-applicable

Specific provisions in terms of protecting people or the environment:

It is recommended to use the information included in this safety data sheet as data used in a risk evaluation of the local circumstances in order to establish the necessary risk prevention measures for the manipulation, use, storage and disposal of this product.

Other legislation:

The product could be affected by sectorial legislation

15.2 Chemical safety assessment:

The supplier has not carried out evaluation of chemical safety.

SECTION 16: OTHER INFORMATION

Legislation related to safety data sheets:

This safety data sheet has been designed in accordance with ANNEX II-Guide to the compilation of safety data sheets of Regulation (EC) Nº 1907/2006 (Regulation (EU) Nº 453/2010, Regulation (EC) Nº 2015/830)

Modifications related to the previous security card which concerns the ways of managing risks. :

Non-applicable

Texts of the legislative phrases mentioned in section 2:

H315: Causes skin irritation
H319: Causes serious eye irritation

Texts of the legislative phrases mentioned in section 3:

The phrases indicated do not refer to the product itself; they are present merely for informative purposes and refer to the individual components which appear in section 3

- CONTINUED ON NEXT PAGE -

SECTION 16: OTHER INFORMATION (continue)

CLP Regulation (EC) nº 1272/2008:

Eye Irrit. 2: H319 - Causes serious eye irritation
Skin Irrit. 2: H315 - Causes skin irritation

Classification procedure:

Skin Irrit. 2: Calculation method
Eye Irrit. 2: Calculation method

Advice related to training:

Minimal training is recommended to prevent industrial risks for staff using this product, in order to facilitate their comprehension and interpretation of this safety data sheet, as well as the label on the product.

Principal bibliographical sources:

http://esis.jrc.ec.europa.eu
http://echa.europa.eu
http://eur-lex.europa.eu

Abbreviations and acronyms:

- ADR: European agreement concerning the international carriage of dangerous goods by road
-IMDG: International maritime dangerous goods code
-IATA: International Air Transport Association
-ICAO: International Civil Aviation Organisation
-COD: Chemical Oxygen Demand
-BOD5: 5-day biochemical oxygen demand
-BCF: Bioconcentration factor
-LD50: Lethal Dose 50
-CL50: Lethal Concentration 50
-EC50: Effective concentration 50
-Log-POW: Octanol–water partition coefficient
-Koc: Partition coefficient of organic carbon

- END OF SAFETY DATA SHEET -

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*.

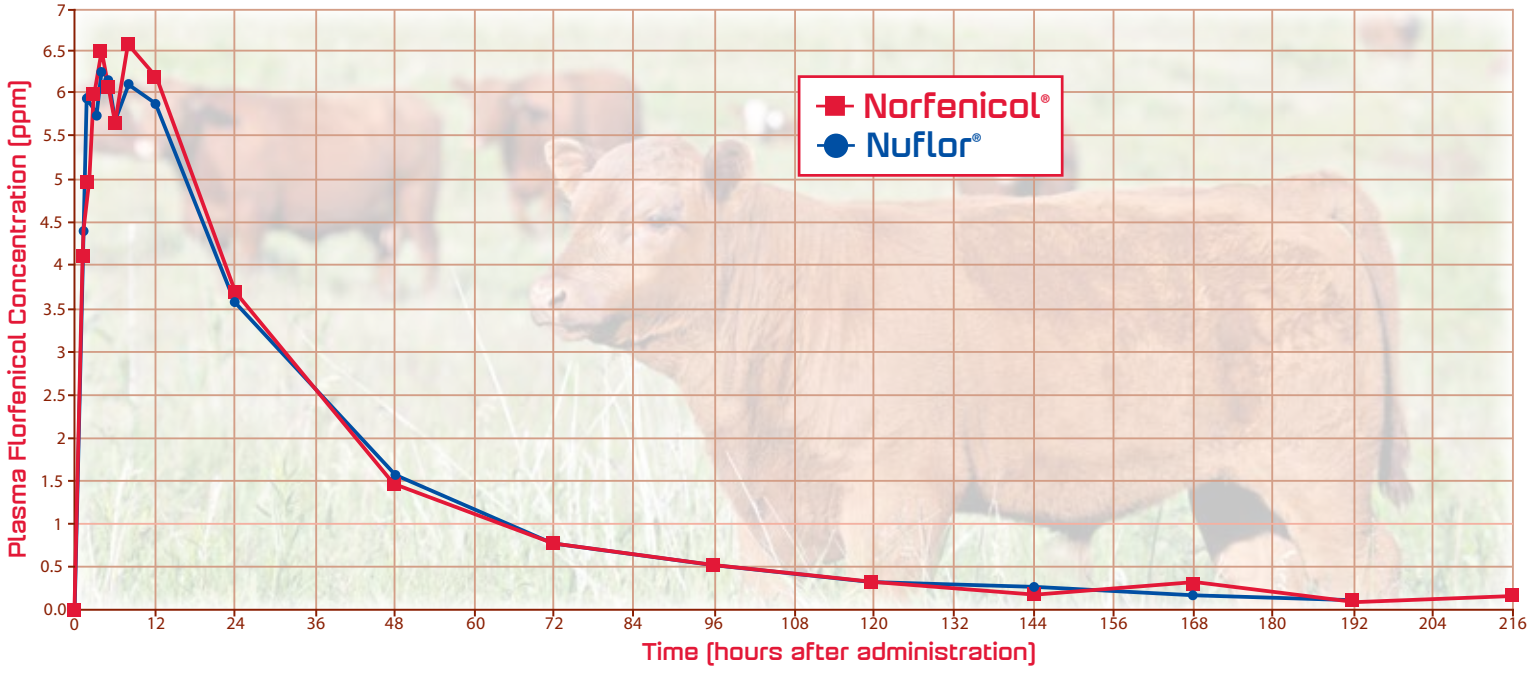
Q. What makes Norfenicol® effective when treating BRD?

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 adminstration. 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 Adminstration 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.

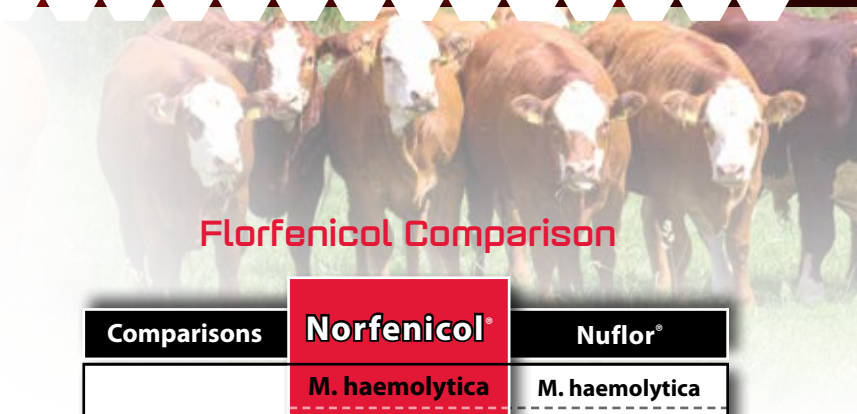
Norfenicol Injectable Solution Dosage Guide

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.



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

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.

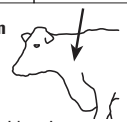
For control of respiratory disease in cattle at high-risk of developing BRD: Norfenicol Injectable Solution should be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (6 mL/100lbs). Do not administer more than 10 mL at each site. The injection should be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

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 susceptible 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.

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Manufactured by: Norbrook Laboratories Limited, Newry,BT35 6PU, Co. Down, Northern Ireland.

Norbrook®

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March 2015

0816-591-I01B