Date of Approval: July 28, 2015

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-591

NORFENICOL

Florfenicol

Injectable Solution

Beef and Non-lactating Dairy Cattle

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*

For the control of respiratory disease in cattle at high risk of developing BRD associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni*

Sponsored by:

Norbrook Laboratories, Ltd.

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I. GENERAL INFORMATION:

A. File Number

ANADA 200-591

B. Sponsor

Norbrook Laboratories, Ltd.
Station Works
Newry BT35 6JP, Northern Ireland

Drug Labeler Code: 055529

US Agent Name and Address:
S. Lee Whaley
Norbrook, Inc.
9401 Indian Creek Parkway, Suite 680
Overland Park, KS 66210

C. Proprietary Name

NORFENICOL

D. Product Established Name

florfenicol

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Injectable solution

G. Amount of Active Ingredient

300 mg/mL

H. How Supplied

100, 250, and 500 mL vials

I. Dispensing Status

Rx

J. Dosage Regimen

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.

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/100 lbs). Do not administer more than 10 mL at each site. The injection should be given only in the neck.

K. Routes of Administration

Intramuscular, subcutaneous

L. Species/Class

Beef and non-lactating dairy cattle

M. Indications

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*.

N. Reference Listed New Animal Drug

NUFLOR Injectable Solution; florfenicol; NADA 141-063; Intervet, Inc.

II. BIOEQUIVALENCE:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, an abbreviated new animal drug application (ANADA) may be submitted for a generic version of an approved new animal drug (reference listed new animal drug (RLNAD)). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

For this ANADA, two *in vivo* blood-level studies were conducted to demonstrate product bioequivalence using the generic and RLNAD florfenicol 300 mg/mL injectable solution. One study was conducted using the intramuscular (IM) route of administration, and one was conducted using the subcutaneous (SC) route of administration. The study information is summarized below.

A. Intramuscular Route Blood-level Bioequivalence Study

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of florfenicol injectable solution 300 mg/mL administered intramuscularly.

1. Title:
   "A pharmacokinetic study to determine the plasma levels of florfenicol in cattle following the intramuscular administration of a formulation of Florfenicol Injection (Norbrook Laboratories Limited, Product Code, P-FFL-100) and NUFLOR Injectable Solution (Intervet, Inc., NADA 141-063)."

2. Testing Facilities:
   Analytical test facility:
   Norbrook Laboratories, Ltd., Research Division, Newry, Co. Down, Northern Ireland.

   In-life test facility:
   Ballyedmond Castle Farms Limited, Rostrevor, Co. Down, Northern Ireland.

3. Objective:
   To determine the plasma concentrations of florfenicol in cattle following IM administration of NORFENICOL Injectable Solution, Norbrook Laboratories, Ltd., Product Code P-FFL-100 (test treatment) and NUFLOR Injectable Solution, Intervet, Inc., Product code NADA 141-063 (control treatment) in cattle and to compare and evaluate the bioequivalence of the products by assessment of the confidence intervals for $AUC_{0\text{-}LOQ}$ and C_{MAX}.

4. Animals
   20 castrated male cattle

5. Experimental Design
   The study was conducted as a randomized, single dose, two-period, two-treatment, crossover design with a 9 day washout interval between study periods.

6. Treatment
   In each period, generic NORFENICOL Injectable Solution or NUFLOR Injectable Solution (RLNAD) was administered via the IM route at a dose of 20 mg/kg per kg of body weight.

7. Measurement and Observation
   The plasma concentrations of florfenicol were measured using a validated bioanalytical method. Pharmacokinetic parameters were determined for each animal individually in each period. Animal observations were made throughout the study for assessment of general health, adverse events, and injection site reactions. All animals remained healthy during the study. No adverse events or injection site reactions were recorded.

8. Statistical Methods
   Blood level bioequivalence was assessed based on measured plasma florfenicol concentrations for the area under the curve from time 0 to the first value below the lower limit of quantification ($AUC_{0\text{-}LOQ}$), observed maximum concentration (C_{MAX}), and time of C_{MAX} (T_{MAX}). For analysis, $AUC_{0\text{-}LOQ}$ and C_{MAX} were logarithmically (natural log) transformed to $LAUC_{0\text{-}LOQ}$ and LC_{MAX}, respectively. A linear mixed effects model containing treatment, sequence, and period as fixed effects, and animal within sequence as a random effect was used to analyze LC_{MAX} and $LAUC_{0\text{-}LOQ}$. Confidence intervals for the ratio of the two treatments were based on back-transforming the endpoints of the 90% confidence interval for the difference between the two treatments for both $LAUC_{0\text{-}LOQ}$ and LC_{MAX}. The endpoints were compared to the acceptance range of 80% to 125% for bioequivalence evaluation. Table 1 below provides the back transformed results for $AUC_{0\text{-}LOQ}$ and C_{MAX}, and the arithmetic means for T_{MAX}. $AUC_{0\text{-}LOQ}$ and C_{MAX} are within the prescribed bounds of 80% to 125%. T_{MAX} values obtained for the test article and RLNAD indicate that these drugs will provide equivalent therapeutic results.

   Table 1: Intramuscular Route Bioequivalence Evaluation

Variable	Generic	RLNAD	Low Bound (%)	Upper Bound (%)
$AUC_{0\text{-}LOQ}$ (mcg/mL)*h	146.11†	149.58†	97.13	107.97
C_{MAX} (mcg/mL)	3.6†	3.8†	94.17	117.46
T_{MAX} (h)	7.1‡	6.5‡	N/A	N/A

† Geometric mean
‡ Arithmetic mean

9. Conclusion
   The generic florfenicol injectable solution is bioequivalent to the RLNAD (NUFLOR Injectable Solution) for $AUC_{0\text{-}LOQ}$ and C_{MAX} when administered via intramuscular injection to cattle at a dose of 20 mg/kg body weight.

B. Subcutaneous Route Blood-level Bioequivalence Study

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of florfenicol injectable solution 300 mg/mL administered subcutaneously.

1. Title:
   "A pharmacokinetic study to determine the plasma levels of florfenicol in cattle following the subcutaneous administration of a formulation of Florfenicol Injection (Norbrook Laboratories Limited, Product Code, P-FFL-100) and NUFLOR Injectable Solution (Intervet, Inc., NADA 141-063)."

2. Testing Facilities:
   Analytical test facility:
   Norbrook Laboratories, Ltd., Newry, Co. Down, Northern Ireland.

In-life test facility:
Ballyedmond Castle Farms Limited, Rostrevor, Co. Down, Northern Ireland.

3. Objective:
To determine the plasma concentrations of florfenicol in cattle following SC administration of NORFENICOL Injectable Solution, Norbrook Laboratories, Ltd., Product Code P-FFL-100 (test treatment) and NUFLOR Injectable Solution, Intervet, Inc., Product code NADA 141-063 (control treatment) in cattle and to compare and evaluate the bioequivalence of the products by assessment of the confidence intervals for $AUC_{0\text{-}LOQ}$ and C_{MAX}.

4. Animals
16 castrated male cattle

5. Experimental Design
The study was conducted as a randomized, single dose, two-period, two-treatment, crossover design with a 28 day washout interval between study periods.

6. Treatment
In each period, generic NORFENICOL Injectable Solution or NUFLOR Injectable Solution (RLNAD) was administered via the SC route at a dose of 40 mg per kg of body weight.

7. Measurement and Observation
The plasma concentrations of florfenicol were measured using a validated bioanalytical method. Pharmacokinetic parameters were determined for each animal individually in each period. Animal observations were made throughout the study for assessment of general health, adverse events, and injection site reactions. All animals remained healthy during the study. There were no adverse events reported in the study with the exception of mild injection site swelling and/or hardness which resolved during the study.

8. Statistical Methods
Blood level bioequivalence was assessed based on measured plasma florfenicol concentrations for the area under the curve from time 0 to the first value below the lower limit of quantification ($AUC_{0\text{-}LOQ}$), observed maximum concentration (C_{MAX}), and time of C_{MAX} (T_{MAX}). For analysis, $AUC_{0\text{-}LOQ}$ and C_{MAX} were logarithmically (natural log) transformed to $LAUC_{0\text{-}LOQ}$ and LC_{MAX}, respectively. A linear mixed effects model containing treatment, sequence, and period as fixed effects, and animal within sequence as a random effect was used to analyze LC_{MAX} and $LAUC_{0\text{-}LOQ}$. Confidence intervals for the ratio of the two treatments were based on back-transforming the endpoints of the 90% confidence interval for the difference between the two treatments for both $LAUC_{0\text{-}LOQ}$ and LC_{MAX}. The endpoints were compared to the acceptance range of 80% to 125% for bioequivalence evaluation. Table 2 below provides the back transformed results for $AUC_{0\text{-}LOQ}$ and C_{MAX}, and the arithmetic means for T_{MAX}. $AUC_{0\text{-}LOQ}$ and C_{MAX} are within the prescribed bounds of 80% to 125%. T_{MAX} values obtained for the test article and RLNAD indicate that these drugs will provide equivalent therapeutic results.

Table 2: Subcutaneous Route Bioequivalence Evaluation

Variable	Generic	RLNAD	Low Bound (%)	Upper Bound (%)
$AUC_{0\text{-}LOQ}$ (mcg/mL)*h	256.39†	251.49†	95	109
CMAX (mcg/mL)	6.97†	7.11†	86	112
TMAX (h)	6.8‡	5‡	N/A	N/A

† Geometric mean
‡ Arithmetic mean

10. Conclusion

The generic florfenicol injectable solution is bioequivalent to the RLNAD (NUFLOR Injectable Solution) for $AUC_{0\text{-}LOQ}$ and C_{MAX} when administered via subcutaneous injection to cattle at a dose of 40 mg/kg body weight.

III. EFFECTIVENESS:

CVM did not require effectiveness studies for this approval.

IV. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this approval.

V. HUMAN FOOD SAFETY:

The following are assigned to this product for cattle:

A. Acceptable Daily Intake and Tolerances for Residues:

The Acceptable Daily Intake (ADI) for total residues of florfenicol is 10 µg/kg BW/day. The tolerances established for the RLNAD apply to the generic product. A tolerance of 3.7 ppm is established for florfenicol amine (the marker residue) in liver (the target tissue), and 0.3 ppm in muscle under 21 CFR 556.283.

B. Withdrawal Period:

Tissue Residue Depletion Study to Determine the Withdrawal Period

Study Title: "A tissue residue study to determine levels of florfenicol (measured as florfenicol amine) in cattle 14, 21, 28, 35 and 42 days following the subcutaneous administration of Florfenicol Injection" (Norbrook Laboratories Limited, Product code P-FFL-100).

Study Directors: M. Ciupitu, B.Sc. and P. Glass, B.Sc.

Study Dates: January 30, 2013, to October 30, 2013

In-life Facility: Ballyedmond Castle Farms Limited (animal facility for Norbrook Laboratories, Ltd.), Rostrevor, Northern Ireland
Analytical Laboratory: Norbrook Laboratories, Ltd., Newry, Northern Ireland

Test Material: Formulation of Florfenicol Injectable Solution (Norbrook Laboratories, Ltd., product Code P-FFL-100), nominally containing 300 mg/mL florfenicol

Study Animals: Twenty-two cattle, 11 males and 11 females, aged approximately between 8-12 months and weighing between 251-302 kg at the time of dosing, were used in the study.

Study Design: Cattle were treated with a single subcutaneous injection into the neck containing 40 mg florfenicol/kg bodyweight. Animals were slaughtered by captive bolt followed by exsanguination at 14, 21, 28, 35, and 42 days following administration. Following slaughter, tissue samples of liver, loin muscle and muscle from the administration site (core and surrounding ring) were removed and samples were assayed for florfenicol amine, the marker residue for florfenicol, using a validated HPLC assay.

Results:

Table 3. Mean florfenicol amine concentrations (ppm) in liver, muscle, injection site core (IS Core), and injection site surrounding ring (IS Ring) in cattle after a single subcutaneous injection of 40 mg florfenicol/kg body weight.

Withdrawal Period (days)	Florfenicol amine (ppm) in Liver	Florfenicol amine (ppm) in Muscle	Florfenicol amine (ppm) in IS Core	Florfenicol amine (ppm) in IS Ring
14	7.08	0.161	51.3	0.311
21	4.56	0.110	1.00	0.113
28	1.62	0.108*	0.248	0.157*
35	1.23	0.136*	0.147	0.139
42	0.81	< 0.100	0.118	0.116

* Only one value above LOQ
LOQ: 0.1 ppm

The calculated statistical tolerance limit for florfenicol amine (the marker residue) in liver (the target tissue) for 99% of the population at 95% confidence is consistent with assigning a 33-day withdrawal period for the subcutaneous administration of NORFENICOL Injectable Solution in cattle at a rate of 40 mg florfenicol/kg bodyweight on one occasion.

Because the withdrawal time for NORFENICOL Injectable Solution following subcutaneous administration is less than the 38 days currently approved for the subcutaneous administration of RLNAD product, and that subcutaneous administration represented the worst case with regard to residue depletion, a 28-day withdrawal period (the withdrawal period assigned for intramuscular administration of the RLNAD) is assigned for intramuscular administration of NORFENICOL Injectable Solution.

C. Regulatory Method for Residues:

The method for determination of florfenicol in cattle liver is a high performance liquid chromatography (HPLC) method.

The validated regulatory method for the determination and confirmation of residues of florfenicol is on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

VI. USER SAFETY:

CVM did not require user safety studies for this approval.

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to NORFENICOL:

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.

VII. AGENCY CONCLUSIONS:

This information submitted in support of this ANADA satisfies the requirements of section 512(n) of the Federal Food, Drug, and Cosmetic Act and demonstrates that NORFENICOL, when used according to the label, is safe and effective.

Additionally, data demonstrate that residues in food products derived from species treated with NORFENICOL will not represent a public health concern when the product is used according to the label.