Date of Approval: May 25, 2018

# FREEDOM OF INFORMATION SUMMARY

## SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-063

Nuflor®

(florfenicol)

Injectable Solution

Cattle (Beef and Non-lactating Dairy)

To provide information to address the human food safety of N-methyl-2-pyrrolidone (NMP) in the formulation of Nuflor® injectable solution in cattle.

Sponsored by:

Intervet, Inc.

# Table of Contents

# I. GENERAL INFORMATION

## A. File Number

NADA 141-063

## B. Sponsor

Intervet, Inc.
2 Giralda Farms
Madison, NJ 07940

Drug Labeler Code: 000061

## C. Proprietary Name

Nuflor®

## 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 mL, 250 mL, and 500 mL glass sterile multiple-dose vials

## I. Dispensing Status

Rx

## J. Dosage Regimen

For treatment of bovine respiratory disease (BRD) and bovine interdigital phlegmon (foot rot): NUFLOR Injectable Solution should be administered by intramuscular injection to cattle at a dose rate of 20 mg/kg body weight (3 mL/100 lbs). A second dose should be administered 48 hours later. Alternatively, NUFLOR Injectable Solution can be administered by a single subcutaneous (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: NUFLOR Injectable Solution should be administered by a single subcutaneous injection to cattle at a dose rate of 40 mg/kg body weight (6 mL/100 lbs). Do not administer more than 10 mL at each site. The injection should be given only in the neck.

**K. Route of Administration**

For treatment of BRD and bovine interdigital phlegmon (foot rot): intramuscular or subcutaneous

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

**L. Species/Class**

Cattle (beef and non-lactating dairy)

**M. Indication**

NUFLOR 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*.

**N. Effect of Supplement**

This supplement provides information to address the safety of N-methyl-2-pyrrolidone (NMP), an excipient in the formulation of Nuflor® injectable solution in cattle. The FOI Summary for the original approval of NADA 141-063 dated May 31, 1996, contains a summary of studies to describe the non-carcinogenic toxicity of NMP in the human diet. Studies subsequently reported in the literature have shown that NMP induced liver cancer in mice. This supplement establishes a level of NMP residues in cattle below which there will not be carcinogenic residues that represent a significant risk of cancer in the human diet.

## II. EFFECTIVENESS

**A. Dosage Characterization**

This supplemental approval does not change the previously approved dosages. The Freedom of Information (FOI) Summaries for the original approval of NADA 141-063 dated May 31, 1996, and a supplemental approval dated June 4, 1998, contains dosage characterization information for cattle.

**B. Substantial Evidence**

CVM did not require effectiveness studies for this supplemental approval. The FOI Summaries for the original approval of NADA 141-063 dated May 31, 1996, and supplemental approvals dated June 4, 1998, December 17, 1998, and January 14,

1999, contain a summary of studies that demonstrate effectiveness of the drug for BRD and foot rot in cattle.

## III. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval. The FOI Summaries for the original approval of NADA 141-063 dated May 31, 1996, and a supplemental approval dated June 4, 1998, contain a summary of target animal safety studies for cattle.

## IV. HUMAN FOOD SAFETY

### A. Antimicrobial Resistance

CVM did not require additional information on microbial food safety (antimicrobial resistance) for this supplemental approval. The FOI Summary for the original approval of NADA 141-063 dated May 31, 1996, contain a summary of human food safety studies for Nuflor® injectable solution in cattle.

### B. Effects of Residues on Human Intestinal Flora

CVM did not require additional information on effects of residues on human intestinal flora for this supplemental approval. The FOI Summary for the original approval of NADA 141-063 dated May 31, 1996, contain a summary of human food safety studies for Nuflor® injectable solution in cattle.

### C. Toxicology

Florfenicol

Reassessment of the toxicological acceptable daily intake (ADI) for florfenicol was not needed for this supplemental approval. The FOI Summary for the original approval of NADA 141-063 dated May 31, 1996, contains a summary of all toxicology studies and information.

N-methyl-2-pyrrolidone (NMP)

1. Summary of Toxicology Studies

The following studies together with the studies in the original approval of NADA 141-063 were considered in establishing the mode of action (how NMP is thought to cause cancer in mice) and the threshold (the amount of NMP that will not cause cancer in mice) for liver carcinogenesis of NMP, an excipient used in Nuflor® injectable solution.

a. *In Vivo* Mechanistic Study – PPARα and CAR activation

**Title:** A 1-week Study of N-Methyl-2-Pyrrolidone (NMP) by Oral Gavage Administration in Mice

**Study Number:** 20032029

**Report Number:** TT# 12-9046

**Report Date:** September 24, 2013

**Study Location:** Spencerville, Ohio

**Study Design:** B6C3F1 mice (5 animals/sex/dose) were orally administered by gavage the test article, NMP, at 0, 1000, and 3000 mg/kg bw/day for 7 consecutive days to evaluate the mode-of-action for NMP-induced hepatic carcinogenesis in this GLP study. A positive control Peroxisome Proliferator Activated Receptor Alpha (PPARα) agonist group (5 animals/sex) was administered in drinking water, trichloroacetic acid (TCA), at 300 mg/kg bw/day. General observations and clinical signs were performed. Body weight and water consumption were recorded. At termination of the study, liver tissue samples were collected from all animals for biochemical and molecular analyses, necropsy examinations were performed, and organ weights for brain and liver were obtained. Histopathological evaluations were conducted on livers from all animals.

**Results and Conclusion:** All mice survived until termination of the study. Decreased activity, few feces, urine staining, dehydration, and distended abdomen were noted at the high dose of NMP (3000 mg/kg bw/day). An absolute mean body weight decrease (~9%) was noted at both 1000 and 3000 mg/kg bw/day for females. No body weight changes in males occurred during the study. There were treatment-related increases in liver weight, both absolute and relative to brain or body weight, in females at 3000 mg/kg bw/day. Centrilobular hypertrophy of the hepatocytes and increased mitotic figures were observed in all animals in the 3000 mg/kg bw/day group. Males showed an increase in the number of hepatocytes undergoing mitosis in the 1000 mg/kg bw/day dose group. NMP treatment (3000 mg/kg bw/day) resulted in a 10.9-fold induction of RNA expression of cytochrome P450 2b10 (indicator of Constitutive Androstane Receptor (CAR) mediated response) in males and 4.3-fold in females. RNA expression of cytochrome P450 4a10 (indicator of PPARα response) was induced 2.9-fold in males and unchanged in females at 3000 mg/kg bw/day. The positive control, TCA, a known hepatocarcinogen, produced expected results of PPARα activation and little or no change in indicators of CAR activation. These results provide evidence that activation of PPARα and CAR may lead to induced cellular proliferation, liver hypertrophy with Cyp2b induction, increased mitotic figures and liver weights, which are some of the key events in the progression of NMP-induced hepatocarcinogenesis in mice.

b. *In Vivo Mechanistic* Study – Liver Enzyme Induction

**Title:** N-Methylpyrrolidone - Liver Enzyme Induction Study in B6C3F1 Mice Administration in the Diet for 2 Weeks

**Report Number:** 99C0225/93071

**Report Date:** February 27, 2002

**Study Location:** Ludwigshafen/Rhein, Germany

**Study Design:** This GLP study was conducted to determine enzyme induction or peroxisome proliferation in the liver after NMP treatment. NMP was administered in the diet for 2 weeks to groups of 10 male and 10 female B6C3F1 mice at the diet concentration of 7200 ppm (mean NMP intake of 1,364 mg/kg bw/day in males and 1,945 mg/kg bw/day in females). A control group was given diet alone for 2 weeks. Clinical observations, food consumption, qualitative water consumption, and body weights were recorded. Cytochrome P450-content (CYP450), ethoxyresorufin-*O*-deethylase (EROD), and pentoxyresorufin-*O*-dependentylase (PROD) activities were obtained by pooling 2 livers from each group. A satellite group of 5 male and 5 female mice were treated for 2 weeks and cyanide-insensitive palmitoyl-CoA-oxidation (Pal-CoA) and light and electron microscopy of liver samples for peroxisome, endoplasmic reticulum or mitochondrial changes were evaluated to correlate with enzyme induction.

**Results and Conclusion:** After treatment for 2 weeks, cyanide-insensitive Pal-CoA activity in the liver was increased in males. Slight or minimal increases in the number of peroxisomes of two treated males were determined in some of the zone 3 hepatocytes. Dark yellow urine was observed in the bedding. No other treatment-related effects were observed. In conclusion, NMP caused a minor increase in peroxisome proliferation in the livers of male mice after 2 weeks of oral exposure.

c. *In Vivo* Mechanistic Study – Hepatic DNA Synthesis and Cell Proliferation

**Title:** N-Methylpyrrolidone - S-phase Response Study in the Liver of B6C3F1 Mice Administration in the Diet for 1 and 4 Weeks

**Report Number:** 99C0225/93070

**Report Date:** January 4, 2002

**Study Location:** Ludwigshafen/Rhein, Germany

**Study Design:** This GLP study was conducted to determine DNA-synthesis/cell proliferation (S-phase response) in the liver after NMP treatment. NMP was administered in the diet for 1 or 4 weeks to groups of 10 male and 10 female B6C3F1 mice at the diet concentration of 7200 ppm (mean NMP intake of 1,392 mg/kg bw/day in males and 1,906 mg/kg bw/day in females). A control group was given diet alone for 4 weeks. Clinical observations, body weight, food consumption, and bromodeoxyuridine (BrdU) incorporation into DNA by immunohistochemistry were obtained. Apoptotic cells numbers were determined by TUNEL-stain.

**Results and Conclusion:** After treatment for 1 week, the males had a 6.9-fold increase in liver cell proliferation and females had a 3.3-fold increase. Mitotic figures were also increased in the male livers. Minimal or slight centrilobular hepatocellular hypertrophy in males (9/10) and in one female (1/10) were observed. Less pronounced fat storage in the liver of males or loss of fat storage in the liver of females were reported. Liver

weights were decreased in females (-13%). After 4-weeks treatment, body weight was decreased in males (-5%). A 2.1-fold or 1.7-fold increase in liver cell proliferation was observed in males and females, respectively. Minimal or slight centrilobular hepatocellular hypertrophy in males (7/10) and in two females (2/10) were observed. Less pronounced fat storage in the liver of males or loss of fat storage in the liver of females were reported. An increased number of apoptotic cells in the livers of males was observed. Intensively dark yellow urine was observed in the bedding from all treated animals. No other treatment related observations were reported. The study showed an increase in cell proliferation in the liver after treatment with NMP for 1 or 4 weeks.

d. Subchronic Oral Toxicity Study in Rodents

**Title:** 90-Day Subchronic Toxicity Study in Rats and Mice Fed N-Methylpyrrolidone (NMP) Including Neurotoxicity Evaluation in Rats.

**Study Number:** Drug and Chemical Toxicology, 22 (3): 455-480 (1999)

**Report Number:** 60C0225/93053

**Report Date:** November 13, 1995

**Study Location:** Ludwigshafen, Germany

**Study Design:** NMP was administered in the diet for 90 days to groups of 10 male and 10 female B6C3F1 mice at a diet concentration of 0, 1,000, 2,500, or 7,500 ppm (equivalent to 0, 167, 417, or 1250 mg/kg bw/day, respectively, but lacking actual food consumption data, the concentration in ppm was divided by six to approximate the daily dose in mg drug/kg bw/day). Body weight, body weight gain, ophthalmologic examination, clinical chemistry, hematology, organ weights, histopathological examination, and clinical observations were obtained. A satellite 28-day study with 10 male and 10 female mice was performed, as well as, a 90-day study in Crl:CD®BR rats, but are not summarized here because the data were not used for the carcinogenic assessment of NMP.

**Results and Conclusion:** No compound-related effects on mortality, hematologic parameters, body weight, or food consumption were reported. Changes in urine color, but not kidney function were observed at the doses of 417 and 1250 mg/kg bw/day. Changes in cholesterol, triglycerides, calcium, and alkaline phosphatase at 28 days, but not following 90 days of NMP treatment were reported. Liver weights were elevated in males at 417 mg/kg bw/day and in both males and females at 1250 mg/kg bw/day for 90 days. Hepatocellular hypertrophy was noted in both males and females at 417 and 1250 mg/kg bw/day. The no-observed-effect level (NOEL)/no-observed-adverse-effect level (NOAEL) for this study was 167 mg/kg bw/day based on the increased liver weight and increased incidences of centrilobular hepatocellular hypertrophy observed at 417 mg/kg bw/day.

e. Oral Carcinogenicity Study in Mice

**Title:** Chronic Toxicity and Oncogenicity of *N*-methylpyrrolidone (NMP) in Rats and Mice by Dietary Administration.

**Study Number:** Drug and Chemical Toxicology, 24(4):315-338 (2001)

**Report Number:** 76C0225/93065

**Report Date:** July 7, 1999

**Study Dates:** November 27, 1995 - July 11, 1997

**Study Location:** Ludwigshafen, Germany

**Study Design:** NMP was administered in the diet for at least 18 months (78 - 80 weeks) to groups of 50 male and 50 female B6C3F1/CrlBR mice at a diet concentration of 0, 600, 1200, or 7200 ppm (equivalent to 0, 100, 200, or 1200 mg/kg bw/day (lacking actual food consumption data due to spillage from clumping, the concentration in ppm was divided by six to approximate the daily dose in mg drug/kg bw/day). Body weight, body weight gain, clinical chemistry, hematology, organ weights, histopathological examination, and clinical observations were obtained. A 2-year study in Crl:CD® (SD)BR rats was also described, but is not summarized here because the data were not used for the carcinogenic assessment for NMP.

**Results and Conclusion:** Administration of the test article resulted in an increase in the incidence of liver tumors and foci of cellular alteration in the liver of both male and female mice receiving the highest dose. Centrilobular hypertrophy of the hepatocytes was noted in most males in this group and correlated with the significant increase in liver weight changes. At 1,200 ppm, relative liver weights were increased in the males, and three males had centrilobular hypertrophy. The effects in the liver were interpreted as a consequence of enzyme induction.

In conclusion, under the conditions of this study, tumorigenic effects were associated with the administration of the test article, NMP. The incidences of both benign and malignant liver tumors and preneoplastic liver lesions (foci of cellular alteration) were increased in male and female mice receiving 7,200 ppm compared to control mice. A NOEL/NOAEL of 600 ppm (100 mg/kg body weight/day) is established for this study based on centrilobular hypertrophy of hepatocytes and renal lipid vacuole formation observed in mid- and high-dose male mice.

f. Non-pivotal *In Vitro* Mechanistic Assays

**Title:** Peroxisome Proliferator Activated Receptor Alpha (PPARα) and Constitutive Androstane Receptor (CAR) Potential of N-Methylpyrrolidone and Various Reference Compounds in Transiently Transfected Chinese Hamster Ovary (CHO) Cells

**Report Numbers:** Mouse PPARα TT#: 12-9049; Rat PPARα TT#: 12-9050; Mouse CAR TT#: 13-9009; Rat CAR TT#: 13-9010; Mouse CAR reference compounds TT#13-9026; Rat CAR reference compounds TT#13-9027

**Report Date:** May 6, 2014

**Study Location:** State College, Pennsylvania

**Study Design:** This investigational study was conducted at an academic university and did not comply with GLP regulations. The potential for NMP to activate PPARα and CAR receptors using a reporter gene assay in transiently transfected CHO cells was performed. Both the mouse and rat nuclear receptors were tested in the assay. The reporter gene was fused to firefly luciferase gene to measure Relative Light Units of activity. Cells were incubated with NMP dissolved in 0.2% dimethyl sulfoxide at concentrations ranging from 9.77 to 5000 µM for PPARα and 2.4 to 5000 µM for CAR for 24 hours at 37 °C. Fourteen reference compounds were used to calibrate the assay.

**Results and Conclusion:** NMP did not demonstrate any significant activation of the rat or mouse PPARα or CAR receptors under the conditions of the assays up to the highest concentration tested (5000 µM). Because NMP is reported to be a weak agonist for PPARα and CAR, it is likely that the *in vitro* assay was either not sufficiently sensitive or not performed under conditions able to detect weak response from the receptors. The data did not support nor contradict the mode of action for NMP to activate PPARα or CAR activity and thus, did not provide key evidence for establishing the mode of action.

2. Summary of Carcinogenic Mode of Action

According to 21 CFR § 500.84(c)(1), FDA considers that "no residue" of a compound remains in edible tissues when the residue of carcinogenic concern in the total diet of people does not exceed the concentration of the test compound in the total diet of test animals that corresponds to a maximum lifetime risk of cancer in the test animals of 1 in 1 million. The sponsor has petitioned a waiver of requirements according to 21 CFR § 500.90 and has explained the reasons why alternative procedures will provide the basis for concluding that approval of the compound satisfies the requirements of the anticancer provisions of the Federal Food, Drug, and Cosmetic Act. Based on the non-genotoxic mode of action summarized below, the alternative approach to the regulation for carcinogenic residues of NMP in the human diet is scientifically acceptable.

NMP was not genotoxic in a battery of genotoxicity studies. However, NMP administration resulted in increased liver weight and hepatocellular hypertrophy and induced liver tumors in B6C3F1/CrlBR mice in an 18-month dietary oncogenicity study. The pleiotropic effects of increased liver weight and hepatocellular hypertrophy are known hallmarks of PPARα and CAR activation. The weight of evidence from the studies listed above supports both CAR and PPARα mechanisms as a non-genotoxic mode of action for NMP-induced carcinogenesis in the mouse. Based on the results of the mechanistic work, it

appears that CAR is the predominate mode of action with a lesser PPARα component. The strongest evidence comes from the one-week mouse study, in which the elevated liver weights and centrilobular hepatocyte hypertrophy is consistent with the hepatic enzyme induction observed in the subchronic dietary exposure study in mice for 2 weeks described above (see section IV.C.1.b). Also, the 1 week mouse study demonstrated that NMP may induce activation of PPARα and CAR transcriptional responses by determining changes in receptor-regulated genes after dosing. These results clearly show that NMP induces Cytochrome P450 2b10 (Cyp2b10) in male and female mice, a finding consistent with a CAR nuclear receptor-mediated response. Also, the minimal Cytochrome P450 4a10 (Cyp4a10) increase observed in male mice is compatible with a weaker PPARα response, in agreement with the results of the study from B6C3F1 mice administered NMP by diet for 2 weeks where a slight-to-minimal peroxisome proliferation in hepatocytes was observed (see section IV.C.1.b), a hallmark of a PPAR-based mechanism.

Thus, progression of key events for the carcinogenic mode of action associated with the mouse-CAR toxicological-signal would be: mouse-CAR activation, altered gene express, cell proliferation, clonal expansion leading to altered foci, mouse liver tumor. Associated events would include hypertrophy, Cyp2b10 induction and altered apoptosis. The induction of mouse liver tumors by NMP is consistent with the list of key events in the scientific literature on the mode of action, including mouse-PPARα activation, cell proliferation and altered apoptosis, preneoplastic foci, clonal expansion, mouse liver tumors. Associated events would include expression of peroxisomal genes, increased in peroxisome numbers, and increase in peroxisome size.

3. Determination of the Point of Departure for the Carcinogenic Response to NMP

   Based on the available toxicology studies, the NOEL/NOAEL of 167 mg/kg bw/day from the 90-day oral toxicity study in mice [Drug and Chemical Toxicology, 22: 455-480 (1999)] was selected to be the most appropriate point of departure for determining the $S_o$ for chronic human exposure to the NMP residue of carcinogenic concern. 167 mg/kg bw/day is a dose of NMP that does not cause observable adverse effects when orally administered to mice for 90 days.

## D. Establishment of the Final ADI for Florfenicol and $S_o$ for NMP

1. The FOI Summary for the original approval of NADA 141-063 dated May 31, 1996, provides for the determination of the ADI for residues of florfenicol. The final ADI is the toxicological ADI of 10 µg/kg bw/day for total residues of florfenicol derived from the two-generation reproduction study in rats. The codified ADI is listed under 21 CFR 556.283.

2. Residues of Carcinogenic Concern in the Total Human Diet ($S_o$) for NMP

   The $S_o$ is defined as the concentration of a residue of carcinogenic concern in the total human diet that represents no significant increase in the risk of cancer to the human consumer.

The $S_o$ for the residue of NMP is calculated using the following formula based on the NOEL/NOAEL of 167 mg/kg bw/day from the subchronic oral toxicity study in mice as the point of the departure, a safety factor of 100, a total daily diet in humans of 1.5 kg/day, and assuming a 60-kg average human body weight. The safety factor of 100 was applied to account for a 10-fold factor for study duration and a 10-fold factor for human-to-human variability and takes into account that the rodent is either uniquely sensitive to PPAR- and CAR-mediated carcinogenicity, or at least considerably more sensitive than other mammalian species.

$$S_o = \frac{\text{Point of Departure/Safety Factor} \times \text{Human Body Weight}}{\text{Total Food in the Human Diet}}$$

$$= \frac{167 \text{ mg/kg bw/day}/100 \times 60 \text{ kg bw}}{1.5 \text{ kg/day}}$$

$$= 66.8 \text{ mg/kg food in the total diet (66.8 ppm)}$$

The $S_o$ for the NMP residue of carcinogenic concern in the total human diet is 66.8 ppm.

## E. Safe Concentrations for Total Residues of Florfenicol in Edible Tissues and the $S_m$ for the NMP Residue of Carcinogenic Concern in Edible Tissues

1. Safe Concentrations for Total Residues of Florfenicol

   The FOI Summary for the original approval of NADA 141-063 dated May 31, 1996, provides for the determination of safe concentration for total residues of florfenicol. The safe concentrations for total residues of florfenicol in the individual edible tissues of cattle are 2 ppm for muscle, 6 ppm for liver, 12 ppm for kidney, and 12 ppm for fat.

2. The $S_m$ for the NMP Residue of Carcinogenic Concern

   The $S_m$ is the concentration of a residue of carcinogenic concern in a specific edible tissue corresponding to no significant increase in the risk of cancer to the human consumer; FDA will assume that this $S_m$ will correspond to the concentration of residue in a specific edible tissue that corresponds to a maximum lifetime risk of cancer in the test animals of 1 in 1 million (21 CFR § 500.82(b) and § 500.84 (c)(1)). Because not all of the total human diet (1500 g per day) is derived from food-producing animals, a correction for food intake is made in determining the $S_m$. The $S_m$ is calculated based on the $S_o$ (in this case, 66.8 ppm), assuming that up to 500 g per day of the total diet is due to the consumption of meat. Of this 500 g total daily meat consumption, 300 g is assumed to be comprised of muscle, 100 g comprised of liver, 50 g comprised of kidney, and 50 g comprised of fat. Thus, one fifth of the total diet, or (300 g muscle/1500 g total diet), would be comprised of muscle, 1/15 comprised of liver, 1/30 comprised of kidney and 1/30 comprised of fat. For example, the concentration of the NMP residue of carcinogenic concern in muscle, $S_m$ muscle, would be calculated as 66.8 ppm ÷ 1/5, which equals 334 ppm.

Calculation of the $S_m$ for the individual edible tissues (as summarized in Table IV.E.1) is as follows:

$S_m$ muscle = 66.8 ppm $\div (\frac{1}{5})$ = 334 ppm

$S_m$ liver = 66.8 ppm $\div (\frac{1}{15})$ = 1002 ppm

$S_m$ kidney = 66.8 ppm $\div (\frac{1}{30})$ = 2004 ppm

$S_m$ fat = 66.8 ppm $\div (\frac{1}{30})$ = 2004 ppm

**Table IV.E.1. Summary Table of the NMP Residue of Carcinogenic Concern in Edible Tissues of Cattle**

| Edible Tissue | Amount Consumed Per Day | Fraction of Total Diet | $S_m$ |
|---|---|---|---|
| Muscle | 300 g | 1/5 | 334 ppm |
| Liver | 100 g | 1/15 | 1002 ppm |
| Kidney | 50 g | 1/30 | 2004 ppm |
| Fat | 50 g | 1/30 | 2004 ppm |

## F. Residue Chemistry

1. Summary of Residue Chemistry Studies

   a. Total Residue and Metabolism Studies for Florfenicol

   CVM did not require additional total residue and metabolism studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-063 dated May 31, 1996, contains a summary of total residue and metabolism studies for florfenicol (Study No. 90708) and NMP (Study No. 90714).

   b. Comparative Metabolism Studies

   CVM did not require additional comparative metabolism studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-063 dated May 31, 1996, contains a summary of comparative metabolism studies for florfenicol (Study No. 90717) and NMP (Study No. 93707).

   c. Studies to Establish Withdrawal Period

   CVM did not require additional tissue residue depletion studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-063 dated May 31, 1996, and the FOI Summary for the supplemental approval of NADA 141-063 dated June 4, 1998, contain a summary of tissue residue depletion studies for florfenicol (Study Nos. 90709 and 96420, respectively).

A residue depletion study for NMP was not needed because residues of florfenicol deplete more slowly than do residues of NMP.

2. Target Tissue and Marker Residue

The data in the florfenicol total residue study (Study No. 90708, summarized in the FOI Summary for the original approval of NADA 141-063 dated May 31, 1996) demonstrate that residues in liver are more persistent and are present at higher concentrations than residues in the other edible tissues. The target tissue for florfenicol is liver. The marker residue for florfenicol is florfenicol amine.

The data in the NMP total residue study (Study No. 90714, summarized in the FOI Summary for the original approval of NADA 141-063 dated May 31, 1996) demonstrate that residues in liver are more persistent and are present at higher concentrations than residues in the other edible tissues. The target tissue for NMP is liver. The marker residue for NMP is parent NMP.

3. Tolerances and $R_m$

Tolerances of 3.7 ppm and 0.3 ppm for florfenicol amine in cattle liver and muscle, respectively, were established previously (21 CFR 556.283).

The $R_m$ for carcinogenic residues, established for parent NMP, is 700 ppb in cattle liver.

4. Withdrawal Periods

A withdrawal period of 28 days is calculated for florfenicol amine in cattle liver when Nuflor® injectable solution for cattle is administered intramuscularly. A withdrawal period of 38 days is calculated for florfenicol amine in cattle liver when Nuflor® injectable solution for cattle is administered subcutaneously. Withdrawal periods of 28 and 38 days are consistent with the depletion of florfenicol and NMP residues in all edible tissues following treatment with Nuflor® injectable solution for cattle.

## G. Analytical Method for Residues

Florfenicol

The validated analytical method for analysis of residues of florfenicol is on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855. To obtain a copy of the analytical method, please submit a Freedom of Information Summary request to:
https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm.

NMP

The validated regulatory method for NMP is published in 21 CFR 500.1410.

## V. USER SAFETY

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

**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 Safety Data Sheet (SDS) contains more detailed occupational safety information.

For customer service, adverse effects reporting, and/or a copy of the SDS, call 1-800-211-3573.

## VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that Nuflor®, when used according to the label, is safe and effective for treatment of BRD associated with *M. haemolytica*, *P. multocida*, and *H. somni*; for the control of respiratory disease in cattle at high risk of developing BRD associated with *M. haemolytica*, *P. multocida*, and *H. somni*; and for the treatment of bovine interdigital phlegmon (foot rot, acute interdigital necrobacillosis, infectious pododermatitis) associated with *F. necrophorum* and *B. melaninogenicus*. The submitted data also establish a concentration of NMP residues in the edible tissues of cattle below which there will be no carcinogenic residues that represent a significant risk of cancer in the human diet. The data demonstrate that residues in food products derived from species treated with Nuflor® will not represent a public health concern when the product is used according to the label.

### A. Marketing Status

Labeling restricts this drug to use by or on order of a licensed veterinarian. This decision was based on the following factors: (a) adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this product to treat BRD or foot rot, and (b) restricting this drug to use by or on order of a licensed veterinarian should help prevent indiscriminate use which could result in violative tissue residues.

### B. Exclusivity

Nuflor®, as approved in our approval letter, does not qualify for marketing exclusivity under section 512(c)(2)(F) of the FD&C Act.

### C. Supplemental Applications

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

**D. Patent Information:**

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.