Date of Approval: August 19, 2021

CORRECTED FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-063

Nuflor®-S

florfenicol

Solution

Swine, except for nursing piglets and swine of reproductive age intended for breeding

For the treatment of swine respiratory disease associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Salmonella* Choleraesuis, *Streptococcus suis*, *Bordetella bronchiseptica*, and *Glaesserella (Haemophilus) parasuis* in swine except for nursing piglets and swine of reproductive age intended for breeding

Sponsored by:

Intervet, Inc.

Executive Summary

Nuflor®-S (florfenicol) is approved in swine for the treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Salmonella* Choleraesuis, *Streptococcus suis*, *Bordetella bronchiseptica*, and *Glaesserella (Haemophilus) parasuis*. Nuflor®-S is not for use in nursing piglets and swine of reproductive age intended for breeding.

Florfenicol is already approved under other New Animal Drug Applications (NADAs) as both a medicated solution in drinking water and a medicated feed for the treatment of SRD in swine. In addition, Nuflor® (florfenicol) injectable solution is already approved under this NADA to treat various bacterial diseases in cattle. This supplemental approval adds the treatment of SRD in swine to the list of indications for the injectable solution.

Florfenicol is a synthetic, broad-spectrum antibiotic active against many Gram-negative and Gram-positive bacteria isolated from domestic animals. It is in the phenicol class of antibiotics and acts by binding to the 50S ribosomal subunit and inhibiting bacterial protein synthesis. Florfenicol has shown *in vitro* activity against the six bacterial pathogens associated with SRD that are listed on the label for Nuflor®-S.

Proprietary Name	Established Name	Dosage Form	Application Type and Number	Sponsor
Nuflor®-S	Florfenicol	Solution	New Animal Drug Application (NADA) 141-063	Intervet, Inc.

Safety and Effectiveness

The sponsor conducted a multi-site, natural infection, field study in young, crossbred pigs to show that Nuflor® injectable solution treats SRD. Pigs were enrolled if they had clinical signs of SRD, including defined levels of depression and respiratory distress as well as a fever of at least 104.5 °F. Before any pigs were enrolled at each site, evidence of SRD was confirmed by necropsy and microbiological examinations performed on several pigs that met the enrollment criteria. At each study site, pigs in the treated group were administered two intramuscular (IM) injections, given 48 hours apart, of 15 mg/kg body weight florfenicol (as Nuflor® injectable solution). Pigs in the control group were administered an equivalent volume of saline, given as two IM injections 48 hours apart. An animal was considered a treatment success if it had improved clinical signs and a rectal temperature less than 104.5 °F on Day 6.

Compared to the control group, significantly more pigs in the treated group were treatment successes. Non-serious adverse events were observed more frequently in the treated group compared to the control group. These adverse events included mild to moderate perianal or vaginal inflammation, rectal eversion, and abnormal fecal consistency (described as loose, pasty, and gruel-like stool). The signs resolved on their own without medical intervention. The adverse events seen in this study are similar to those associated with other florfenicol products and are described on the label for Nuflor®-S. No injection site irritation was observed during the study.

Because Nuflor®-S is identical to Nuflor® injectable solution, the study showed that Nuflor®-S is effective for the treatment of SRD.

For the microbiology assessment, isolates were collected from pre-treatment lung samples from representative, non-enrolled pigs at each study site and from post-treatment lung samples from pigs in both the treated and control groups that died or were euthanized during the study or were classified as treatment failures on Day 6 (the end of the study). A sufficient number of each pathogen listed on the label for Nuflor®-S were cultured from pigs across the study sites.

The sponsor conducted a safety study in young, healthy male and female crossbred pigs. The pigs were administered florfenicol (as Nuflor® injectable solution) by IM injection at 1X, 3X, or 5X the labeled dose of Nuflor®-S given every 48 hours for a total of six injections. This is three times the labeled duration of two injections given 48 hours apart. Pigs in the control group were given saline at a dose volume equivalent to the 5X group using the same dosage regimen. Another group of pigs was administered florfenicol (also as Nuflor® injectable solution) by IM injection at 10 times the labeled dose of Nuflor®-S at the labeled duration (two treatments given 48 hours apart).

Florfenicol-treated pigs had moderate diarrhea and mild to moderate anal swelling and erythema. Mild to moderate injection site swelling was also observed. This finding was more frequently seen in the higher dose groups. Florfenicol-treated pigs also had decreased feed and water consumption, with a corresponding decrease in body weight. Overall, Nuflor® injectable solution was well-tolerated in all treatment groups. Because Nuflor®-S is identical to Nuflor® injectable solution, the study showed that Nuflor®-S is safe when used according to the label.

The sponsor also conducted an injection site safety study in healthy, young pigs that showed that Nuflor® injectable solution causes mild injection site irritation that may persist up to 21 days after treatment. These reactions may result in trim loss of edible tissue at slaughter. Because Nuflor®-S is identical to Nuflor® injectable solution, the same conclusion applies.

The sponsor did not conduct safety studies for the use of florfenicol in nursing piglets or in swine of reproductive age intended for breeding. Therefore, the label states that Nuflor®-S is not for use in these groups of swine.

User Safety

N-methyl-2-pyrrolidone (NMP), an ingredient in Nuflor®-S, caused reproductive and developmental toxicities in laboratory animals following high, repeated exposures. Because there is a risk of exposure to NMP from accidental injection or dermal exposure in pregnant women who handle Nuflor®-S, the Agency recommends that pregnant women wear gloves and exercise caution when handling Nuflor®-S, or avoid handling the product. The label for Nuflor®-S contains safety information for people who handle, administer, or are exposed to the drug.

Human Food Safety

FDA conducted a human food safety assessment to ensure that any residues of florfenicol and NMP in the edible tissues of treated animals are at a concentration

that present a reasonable certainty of no harm to people when Nuflor®-S is used according to the label. The human food safety evaluation is conducted from the perspectives of microbial food safety, toxicology, and residue chemistry.

For microbial food safety, FDA evaluated a complete, qualitative risk assessment that described florfenicol's antimicrobial characteristics with respect to 1) promoting the emergence or selection of antimicrobial-resistant bacteria of public health concern in or on treated swine; 2) the relative quantities of pork products consumed by people and the bacterial contamination rates of pork products derived from treated swine; and 3) its importance in human medicine. Florfenicol is not used in human medicine; however, another antimicrobial in the phenicol class—chloramphenicol—is used in human medicine. Therefore, FDA assessed the potential for cross-resistance from the use of florfenicol in swine to adversely impact human health. Results from the three components of the risk assessment were integrated into an overall risk estimation of medium for the use of florfenicol in swine, and corresponding medium risk mitigators were applied to the conditions of use for florfenicol.

FDA determined that it was not necessary to reassess the acceptable daily intake (ADI) and safe concentrations for florfenicol or the potential carcinogenicity for NMP. FDA established the ADI for florfenicol as 10 µg/kg body weight/day and the safe concentrations in individual edible tissues of swine as 2 parts per million (ppm) for muscle, 6 ppm for liver, 12 ppm for kidney, and 12 ppm for fat. FDA previously addressed the potential carcinogenic concern of NMP residues by establishing an S_o of 66.8 ppm and S_m values of 334 ppm for muscle, 1002 ppm for liver, 2004 ppm for kidney, and 2004 ppm for fat. The S_o is the concentration of NMP residues of carcinogenic concern in the total human diet that represents no significant increase in the risk of cancer to people. The S_m is the concentration of NMP residues of carcinogenic concern in a specific edible tissue corresponding to no significant increase in the risk of cancer to people.

The sponsor conducted four metabolism studies and one residue depletion study to assess the quantity and nature of the residues in tissues derived from pigs treated with Nuflor®-S. For florfenicol, FDA determined that florfenicol amine is the marker residue and liver is the target tissue. For NMP, FDA determined that parent NMP is the marker residue and liver is the target tissue. FDA used the information from these studies, in combination with the ADI and safe concentrations for florfenicol and the S_o and S_m values for NMP, to establish a tolerance of 2.5 ppm of florfenicol amine in swine liver, an R_m of 88 parts per million of NMP in swine liver, and a tissue withdrawal period of 11 days. The R_m is the concentration of the marker residue (parent NMP) in the target tissue (swine liver) when the residue of carcinogenic concern (NMP residues of carcinogenic concern) is equal to S_m. FDA also established a tolerance of 0.2 ppm for residues of florfenicol amine in swine muscle. FDA evaluated the validated analytical methods and found their use acceptable.

Conclusions

Based on the data submitted by the sponsor for the approval of Nuflor®-S, FDA determined that the drug is safe and effective when used according to the label.

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®-S

D. Drug Product Established Name

florfenicol

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Solution

G. Amount of Active Ingredient

300 mg/mL

H. How Supplied

100 mL vial

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Nuflor®-S Injectable Solution should be administered by intramuscular injection to swine at a dose rate of 15 mg/kg (1 mL/45 lb) body weight. A second dose should be administered 48 hours later.

K. Route of Administration

Intramuscular

L. Species/Class

Swine, except for nursing piglets and swine of reproductive age intended for breeding

M. Indication

For the treatment of swine respiratory disease associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Salmonella* Choleraesuis, *Streptococcus suis*, *Bordetella bronchiseptica*, and *Glaesserella (Haemophilus) parasuis* in swine except for nursing piglets and swine of reproductive age intended for breeding.

N. Effect of Supplement

This supplement provides for use in an additional species (swine) for the indication as provided in Section I.M. above.

II. EFFECTIVENESS

A. Dosage Characterization

A study was conducted in Nebraska in 1995 to establish an effective intramuscular (IM) dose of florfenicol for treatment of swine with swine respiratory disease (SRD). A total of 165 castrated male crossbred pigs, 8 to 12 weeks old, with a mean initial body weight (BW) of 17.4 kg were enrolled in the study. A group of seeder pigs, inoculated with a broth culture of *Actinobacillus pleuropneumoniae*, were commingled with clinically normal candidate pigs to induce an SRD outbreak. Candidate pigs with dyspnea and a rectal temperature of ≥ 104.5 °F were selected for enrollment and treated with Nuflor® injectable solution at 5, 10, 15, or 20 mg/kg BW IM once daily for 3 consecutive days, or two injections of Nuflor® injectable solution at 15 or 20 mg/kg BW IM given 48 hours apart, or saline (negative control). Pigs were observed for clinical signs of SRD (dyspnea and depression) for 10 days after the first injection (Day 0) and then were euthanized for respiratory tract evaluation.

Rectal temperature (measured daily from Days 0 to 10), mortality rate, and lung consolidation score (at necropsy) were the primary variables. All florfenicol group mean temperatures were significantly lower than the saline group mean temperature from Days 1 through 7 except for one evaluation (5 mg/kg BW once daily for 3 consecutive days group on Day 6) where the mean was numerically but not statistically significantly lower. The mortality rate for the saline group (40%) was significantly higher than the mortality rate (0 to 7%) for the florfenicol treated groups. All florfenicol group mean lung consolidation scores (3.6% to 11.4%) were significantly lower than the saline group mean lung consolidation scores (29%) and were not collectively different from one another. Transient, self-limiting perianal irritation and unformed feces were observed in florfenicol-treated pigs. Dosages of 10 mg/kg BW IM once daily for 3 consecutive days or two doses of 15 mg/kg BW IM given 48 hours apart were considered effective in this model.

B. Substantial Evidence

1. Natural Infection Field Study

Title: Evaluation of the Efficacy and Safety of Nuflor® Injectable Solution (15 mg/kg Twice 48 Hours Apart) in the Treatment of Porcine Respiratory Disease Complex (PRDC) by Comparison to a Negative Control and an Alternative Dosing Regimen under Field Conditions. (Study No. C00-199-01, -02, -04, -05, -06, -07, -08, -09, -10, and -13)

Study Dates: March 2001 to March 2002

Study Locations: Story City, IA (two sites); Algona, IA (two sites); St. Peter, MN; Brookings, SD (two sites); Oakland, NE; Frankfort, IN; and Harrisonburg, VA.

Study Design:

Objective: To evaluate the effectiveness of florfenicol administered by IM injection at 15 mg/kg BW, given as two doses 48 hours apart, for the treatment of SRD.

Study Animals: A total of 932 crossbred male and female pigs ranging in age from 6 to 14 weeks and from 8 to 63.1 kg BW were enrolled in the study. Pigs were housed in pens (minimum 4 pigs per pen) constructed or arranged to prevent nose-to-nose contact. Animals were housed in indoor facilities with standard lighting, heating/cooling, and ventilation conditions. Study animals were provided an appropriate non-medicated swine grower diet and had *ad libitum* access to water.

Experimental Design: This was a multi-site natural infection field study. The study was conducted in accordance with good clinical practice guidelines. Animals meeting enrollment criteria (described below) were randomly assigned to one of three treatment groups – florfenicol [proposed dosage regimen] at two doses at 15 mg/kg BW IM 48 hours apart (311 pigs), florfenicol [alternate dosage regimen] at 15 mg/kg BW IM once daily for 3 consecutive days (312 pigs), or an equivalent volume of saline (309 pigs) given as two IM injections 48 hours apart. Treatment groups were not commingled within a pen. The alternate dosage regimen group was not used for the evaluation of effectiveness for the approved conditions of use. The producers, investigators, and the bacteriological laboratory were masked to treatment group assignments.

Drug Administration: The test article was Nuflor® injectable solution (NADA 141-063, 300 mg florfenicol per mL). The negative control article was physiological saline (0.9% sodium chloride) solution. The test and control articles were given by IM injection in the neck on Days 0 and 2 for the florfenicol and saline groups, and on Days 0, 1, and 2 for the alternate dosage regimen group. No concomitant medications were administered.

Measurements and Observations: Pigs were enrolled on Day 0 if they had a rectal temperature of ≥ 104.5 °F, and a depression score (0=absent, 1=mild, 2=moderate, and 3=severe) of ≥ 2, and a dyspnea score (0=absent, 1=mild,

2=moderate, and 3=severe) of ≥ 2. Evidence of SRD was confirmed pre-enrollment via necropsy and microbiological examinations performed at each site on 2 to 7 pigs that met the inclusion criteria. At some sites, nasal swabs were collected on Day 0 prior to treatment for microbiological examination. Rectal temperature, dyspnea, depression, and cough were assessed daily from Day 0 through Day 6; a clinical illness index score was also assigned. Pigs were observed from Day 0 through Day 6 for signs of perianal inflammation, rectal eversion/prolapse, abnormal fecal consistency, injection site irritation, concurrent disease, and other adverse events. Body weights were recorded on Day 0 and Day 6 (or at necropsy). Mortality was recorded from Day 0 through Day 6. Pneumonic lung tissue was collected for microbiological examination from all pigs that died or were euthanized during the study and from all pigs classified as a treatment failure on Day 6. For pneumonic lesions, lung consolidation percentages were estimated by visual inspection and palpation. A microbiological culture and sensitivity to florfenicol was performed on all bacterial isolates.

The primary variable for determination of effectiveness was treatment success rate on Day 6. A pig was classified as treatment success if it had a rectal temperature of < 104 °F, and a depression score of 0 or 1, and a dyspnea score of 0 or 1. Pigs not meeting the criteria for success were classified as treatment failures. Secondary variables (not used for the effectiveness determination and therefore not reported in the results section) were mortality, individual clinical parameters (rectal temperature, depression, and dyspnea), cough, clinical illness index score, and body weight.

Statistical Methods: The experimental unit was pen. The treatment success rates were analyzed using a generalized linear mixed model with treatment as a fixed effect, and site, site-by-treatment interaction, and pen nested within site-by-treatment as random effects. One-sided tests of each test article versus control at alpha of 0.025 were used for analyzing the primary endpoint. For pairwise comparisons of the test articles to the negative control, the Dunnett adjustment was made.

Results: After pen and animal exclusions due to protocol deviations, 561 pigs (101 pens) remained in the primary variable analysis for the two-dose regimen. The treatment success rate was statistically significantly (adjusted $p < 0.0001$) superior in the florfenicol-treated group (72%) compared to the negative control group (33.1%). From microbiologic samples, 100, 107, 36, 62, 49, and 36 isolates of *A. pleuropneumoniae*, *P. multocida*, *S.* Choleraesuis, *S. suis*, *B. bronchiseptica*, and *G. parasuis*, respectively, were identified.

Adverse Reactions: Mild to moderate perianal (or vaginal) inflammation, rectal eversion, and abnormal fecal consistency (described as loose, pasty, and gruel-like stool) were reported more frequently in the florfenicol-treated groups than in the saline-treated group during the study; no cases required medical intervention. No injection site irritation was observed during the study.

Conclusions: This study demonstrates that florfenicol (as Nuflor® injectable solution) administered as two doses of 15 mg/kg BW by IM injection given 48 hours apart is effective for the treatment of SRD associated with *A. pleuropneumoniae*, *P. multocida*, *S.* Choleraesuis*, S. suis*, *B. bronchiseptica*,

and *G. parasuis*. Because Nuflor®-S is identical to Nuflor® injectable solution, the study also demonstrates that Nuflor®-S is effective for these conditions of use.

III. TARGET ANIMAL SAFETY

A. Drug Tolerance and Toxicity Study

Title: Target Animal Safety Study of SCH 25298 (Florfenicol) Injected Intramuscularly in Swine. (Study No. 96320)

Study Dates: June 1997 to November 1997

Study Location: Santa Ysabel, CA

Study Design:

Objective: To assess the safety of florfenicol when administered to swine by IM injection at 0, 1, 3, and 5 times the labeled dose of 15 mg/kg BW given every 48 hours for a total of 6 injections (3 times the labeled duration of two injections 48, hours apart); and at 10 times the labeled dose for two treatments, 48 hours apart.

Study Animals: A total of 40 healthy crossbred pigs (20 males, 20 females), 2 to 4 months of age, weighing 45.5 to 63 kg at the initiation of dosing, were used in the study. Pigs were individually housed in indoor pens and had *ad libitum* access to water and a commercial-type swine grower diet.

Experimental Design: This study was conducted in accordance with FDA Good Laboratory Practice (GLP) regulations (21 CFR Part 58). Within gender, pigs were ranked according to body weight. Four weight blocks, composed of 5 pigs each, were constructed according to ascending body weight. Within a block, each pig was individually housed and randomly assigned to one of five treatment groups (4 males and 4 females per group): a negative control (0X); florfenicol at 15 mg/kg BW (1X), 45 mg/kg BW (3X), or 75 mg/kg BW (5X) as six treatments given 48 hours apart; or florfenicol at 150 mg/kg BW (10X) as two treatments given 48 hours apart. Persons responsible for performing clinical observations and necropsy were masked to treatment assignments.

Drug Administration: The test article was Nuflor® injectable solution (300 mg florfenicol per mL). The negative control article was physiological saline (0.9% sodium chloride) solution, given at a dose volume equivalent to the 5X group. The test and control articles were given by IM injection in the neck (alternating left and right sides) on Days 0, 2, 4, 6, 8, and 10 for the 0X, 1X, 3X, and 5X groups, and on Days 8 and 10 for the 10X group. No concomitant medications were administered. A maximum volume of 10 mL was given at each injection site.

Measurements and Observations: Clinical observations (for survival, general condition, and abnormal health) were conducted once daily from Day -21 through Day 11. Feed and water consumption were measured daily from Day -14 through Day 11. Body weights were measured weekly from Day -21 through Day 11. On

Days -14, -1, 3, 7, and 11, physical examinations were conducted and samples were collected for hematology, coagulation, serum chemistry, urinalysis, and fecal analysis. All pigs were euthanized on Day 12, approximately 48 hours after the final dose, for gross necropsy and histopathology evaluation.

Statistical Methods: Feed and water consumption, body weight, hematology (excluding all differential white cell counts except lymphocytes and segmented neutrophils), and serum chemistries were analyzed using a statistical model with baseline observations included as a covariate. Sex, dose, dose*sex, time, sex*time, dose*time, and sex*dose*time were included as fixed effects, and weight block within sex, the interaction of weight block within sex and dose, and the interaction of weight block within sex and time were included as random effects. The analyses of organ variables had a similar model except that time was not an analysis factor. All fixed effects were tested at the 0.10 level of significance except the three-way interaction term (sex*dose*time), which was tested at the 0.05 level of significance.

Results:

Clinical Observations and Physical Examinations: Test article-related moderate diarrhea and mild to moderate anal swelling/erythema were noted in all florfenicol-treated groups after dosing, most frequently in the 3X (8 pigs) and 5X (6 and 8 pigs, respectively) groups. Mild to moderate injection site swelling, attributed to the test article, was seen in all florfenicol-treated groups beginning on Day 7, most frequently in the 3X (7 pigs) and 5X (8 pigs) groups. While these findings were considered clinically relevant, the incidence and severity in the 1X group was considered within acceptable limits. Vomiting, considered clinically insignificant, was observed sporadically in all florfenicol-treated groups (one pig each in the 1X, 3X and 10X groups and 5 pigs in the 5X group) and in the control group (one pig), with most observations occurring on or after Day 9.

Feed and Water Consumption: Mean feed consumption in the 1X and 10X groups was similar to the control group throughout the study. Mean feed consumption was markedly decreased in the 3X and 5X groups starting on Day 4 compared to the other groups and to pre-treatment values. Similar trends were observed for water consumption. The findings in the 3X and 5X groups were considered test article-related and clinically significant.

Body Weights: Mean body weights in the 1X and 10X groups increased over the study and were similar to the control group. Pigs in the 3X and 5X groups lost weight between Day 5 and Day 11, and mean body weights in these groups were moderately lower compared to the 1X and 10X groups. The findings in the 3X and 5X group were associated with decreased feed consumption and were considered test article-related and clinically significant.

Hematology, Serum Chemistry, and Coagulation: A moderate but clinically insignificant decrease in the white blood cell counts and a slight decrease in lymphocyte numbers were seen in the 5X group, which were considered test article-related. Test article-related, significant, minimal or slight changes were seen in the 3X and 5X groups for sodium (decreased), alkaline phosphatase (decreased), globulin (decreased), and albumin/globulin ratio (increased).

Additionally, changes in chloride (decreased), albumin (increased), and serum urea nitrogen (increased) were seen in the 5X group, and increased creatinine was seen in the 5X and 10X groups. These changes were considered test article-related but were not considered clinically significant. Changes in numerous other parameters were observed but were not considered test article-related because they were not dose-dependent or time-dependent. These changes were also within the range of pre-test values, and/or were of such small magnitude that they were not considered to be clinically significant.

Urine and Fecal Analyses: No drug-related findings were observed. Changes in some parameters (including fecal consistency and occult blood) were observed but were not considered test article-related because they were not dose-dependent or time-dependent.

Gross Necropsy and Histopathology: Test article-related findings included anal swelling/erythema (7 pigs in the 3X or 5X groups) and injection site lesions. Injection site lesions, described as gross discoloration and edema and which correlated microscopically with degeneration, necrosis, inflammation, fibroplasia/fibrosis and/or edema, were noted for animals in all florfenicol-treated groups, generally with a dose-dependent increase in frequency. Gross or microscopic lesions were noted sporadically in other organs/tissues and were considered incidental.

Conclusion: The study demonstrates that florfenicol (as Nuflor® injectable solution) is safe in pigs when given as two doses of 15 mg/kg BW by IM injection 48 hours apart. Because Nuflor®-S is identical to Nuflor® injectable solution, the study also demonstrates that Nuflor®-S is safe for the labeled dosage regimen.

B. Injection Site Irritation Study

Title: Injection Site Irritation Study of SCH 25298 (Florfenicol) Administered Intramuscularly to Swine. (Study No. 97094)

Study Dates: July 1997 to November 1997

Study Location: Santa Ysabel, CA

Study Design:

Objective: To evaluate the resolution of injection site lesions up to 42 days after IM injection of florfenicol given as two doses of 15 mg/kg BW, 48 hours apart. This study was conducted in accordance with FDA GLP regulations (21 CFR Part 58).

Study Animals: A total of 20 healthy crossbred pigs (10 males, 10 females), 2 to 4 months of age, weighing 40 to 64.5 kg on Day -1, were used in the study. Pigs were individually housed in indoor pens and had *ad libitum* access to water and a commercial-type swine grower diet.

Experimental Design: On Day -1, pigs were randomly assigned (with body weight stratification) to one of five treatment groups (2 males and 2 females per

group). The study was conducted using a staggered dosing schedule as shown in Table III.1.:

Table III.1. Treatment Groups, Study 97094

Group	Dosing Days	Days Post-dose at Necropsy (Day 42)
1	Days 0 and 2	42
2	Days 14 and 16	28
3	Days 21 and 23	21
4	Days 28 and 30	14
5	Days 35 and 37	7

Drug Administration: The test article was Nuflor® injectable solution (300 mg florfenicol per mL). No control article was used for this study. The test article was given by IM injection in the neck (alternating left and right sides) to all pigs as two injections of 15 mg/kg BW administered 48 hours apart on the assigned dosing days.

Measurements and Observations: Clinical observations (for survival, general condition, and abnormal health) were conducted once daily from Day -21 through Day 42. Body weights were measured weekly from Day -21 through Day 41. Physical examinations were conducted on Day -14. All pigs were euthanized on Day 42 and subjected to gross necropsy and histopathologic evaluation of the injection sites.

Statistical Methods: No statistical evaluation was conducted.

Results:

Two pigs died during the study. One pig (group 1 female) died on Day 6 with no observed clinical signs; enterotoxemia was suspected. The second pig (group 5 female) died on Day 36 after being observed with decreased body weight, anorexia, ataxia, and intermittent fasciculations of one-week duration; no cause of death was determined. Both deaths were considered incidental. All other pigs remained clinically healthy and gained weight during the study.

Mild injection site swelling was observed in approximately 11% of the pigs one day post-injection, and in up to approximately 32% of the animals by 4 days post-injection. Injection site swelling was clinically resolved by 16 days post-injection.

At necropsy, discoloration of the injection sites was observed in group 4 (14 days post-injection) and group 5 (7 days post-injection), but not in group 3 (21 days post injection). These discolorations correlated microscopically with degeneration, fibrosis/fibroplasia, hemorrhage, inflammation, mineralization and/or necrosis.

Conclusion: This study demonstrates that florfenicol (as Nuflor® injectable solution) given as two doses of 15 mg/kg BW by IM injection 48 hours apart results in mild injection site irritation which may persist up to 21 days and may result in trim loss of edible tissue at slaughter. Because Nuflor®-S is identical to Nuflor® injectable solution, the same conclusion applies.

IV. HUMAN FOOD SAFETY

A. Microbial Food Safety

Background and Outcome of Risk Assessment

The Agency evaluated microbial food safety information and data for florfenicol, "for the treatment of swine respiratory disease associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Salmonella* Choleraesuis, *Streptococcus suis*, *Bordetella bronchiseptica*, and *Glaesserella* (*Haemophilus) parasuis* in swine except for nursing piglets and swine of reproductive age intended for breeding". This product will be administered by intramuscular injection at a dosage of 15 mg/kg body weight (BW), with a second administration at 48 hours, in swine except for nursing piglets and swine of reproductive age intended for breeding. The withdrawal period for this product is 11 days.

The microbial food safety assessment submitted for Agency review included a *release assessment* to describe the probability that florfenicol and its use at 15 mg/kg BW with a second administration at 48 hours will result in the emergence of phenicol-resistant bacteria or resistance determinants in treated swine under proposed conditions of use; an *exposure assessment* to describe the likelihood of human exposure to resistant bacteria or resistance determinants through consumption of edible products from florfenicol-treated swine; and a *consequence assessment* to describe potential human health consequences arising from exposure to defined resistant bacteria or resistance determinants by considering the human medical importance of phenicol antibiotics used in the treatment of human infectious diseases.

The risk assessment included information on florfenicol and chloramphenicol, specifically the spectrum of antibacterial activity, mechanism(s) of florfenicol and chloramphenicol resistance, known antimicrobial resistance-conferring determinants, co-selection for resistance to other medically-important antimicrobials and impact on the development or selection of antimicrobial resistance in Gram-negative and Gram-positive foodborne pathogens of concern (*Salmonella enterica* serotypes, *Campylobacter* spp., *Escherichia coli*, *Enterococcus* spp., and methicillin-resistant *Staphylococcus aureus*) as a result of the use of florfenicol in swine. The risk for compromising antimicrobial therapies for non-foodborne pathogens of concern including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and other drug-resistant *Staphylococcus* spp. was additionally addressed as a result of the use of florfenicol in swine. Florfenicol is not used in human medicine; however, another antimicrobial in the phenicol class - chloramphenicol - is used in human medicine, and the cross-resistance which may result from the use of florfenicol in veterinary medicine which may compromise human therapy was addressed in the risk assessment.

The Agency concludes that use of florfenicol in swine will not result in a significant risk for the development of phenicol resistance in foodborne *Salmonella enterica* serotypes, *Campylobacter* spp., *E. coli*, and *Enterococcus* spp. originating from treated swine, or compromise human therapy to non-foodborne pathogens of concern (*Streptococcus pneumoniae*, *Neisseria meningitidis*, and other drug-resistant *Staphylococcus* spp.). This conclusion is

based upon evaluation of the information submitted by the firm, consideration of the spectrum of activity of florfenicol, the potential of florfenicol to select for the subsequent emergence of antimicrobial resistance in treated swine, the prevalence of the aforementioned zoonotic foodborne pathogens in swine-derived food products, and taking into considerations the following conditions of use for florfenicol:

- Florfenicol is indicated, "for the treatment of swine respiratory disease associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Salmonella* Choleraesuis, *Streptococcus suis*, *Bordetella bronchiseptica*, and *Glaesserella (Haemophilus) parasuis* in swine except for nursing piglets and swine of reproductive age intended for breeding",

- Florfenicol labeling will state, "Nuflor®-S Injectable Solution should be administered by intramuscular injection to swine at a dose rate of 15 mg/kg (1 mL/45 lb) body weight. A second dose should be administered 48 hours later. The injection should be given only in the neck musculature.",

- Florfenicol (Nuflor®-S) will be available by prescription and, therefore, will be administered under veterinary oversight,

- The withdrawal period is 11 days.

Decision Statement: The overall risk estimation associated with the use of florfenicol as delivered to swine *via* injection under the proposed conditions of use is medium, based on individual rankings of medium for the *release assessment*, medium for the *exposure assessment*, and highly important for the *consequence assessment*. The use of florfenicol by injection for swine, with the risk mitigations listed above, should assure the safe use of florfenicol, and in a manner that would mitigate resistance emergence or selection associated with any adverse impact on human health.

B. Toxicology

1. Acceptable Daily Intake (ADI) for florfenicol

   Reassessment of the codified ADI for the active ingredient, florfenicol, was not needed for this supplemental approval. The codified ADI for total residue of florfenicol is 10 µg/kg BW/day, as listed under 21 CFR 556.283. The FOI Summaries for the original approval of NADA 141-063, dated May 31, 1996, and the supplemental approval of NADA 141-246, dated April 4, 2012, contain summaries of all toxicology studies and information for florfenicol.

2. S_o for *N*-methyl-2-pyrrolidone (NMP)

   Reassessment of the S_o for the excipient, NMP, was not needed for this supplemental approval. The S_o, the concentration of NMP residues of carcinogenic concern in the total human diet that represents no significant increase in the risk of cancer to the human consumer, is 66.8 ppm based on the 90-day oral toxicity study in mice [Drug and Chemical Toxicology, 22: 455-480 (1999)]. The FOI Summary for the original approval of NADA 141-063, dated May 31, 1996, and a supplemental approval, dated

May 25, 2018, contain summaries of all toxicology studies and information for NMP.

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

1. Reassessment of the safe concentrations for total residues of florfenicol was not needed for this supplemental approval. The safe concentrations of total residues of florfenicol in individual edible tissues of swine are 2 ppm for muscle, 6 ppm for liver, 12 ppm for kidney, and 12 ppm for fat.

2. Reassessment of the S_m for the NMP residue of carcinogen concern was not needed for this supplemental approval. The S_m is the concentration of NMP residue of carcinogenic concern in a specific edible tissue corresponding to no significant increase in the risk of cancer to the human consumer. The S_m for the NMP residue of carcinogen concern in individual edible tissues of swine are 334 ppm for muscle, 1002 ppm for liver, 2004 ppm for kidney, and 2004 ppm for fat.

D. Residue Chemistry

1. Summary of Residue Chemistry Studies

   a. Total Residue and Metabolism Studies

      Title: SCH 25298 (Florfenicol): A Total Residue Depletion Study Following Intramuscular Administration of NUFLOR to Swine. (Study No. 96363).

      Study Dates: September 19, 1996, to December 23, 1997

      Study Location: Las Cruces, NM

      Objectives: The objectives of the GLP study were to determine the total residue in each edible tissue and injection site of swine, identify the metabolites of florfenicol, identify the marker residue and target tissue, and estimate the excretion in urine and feces after two intramuscular injections of radiolabeled florfenicol 48 hours apart.

      Thirteen cross-bred swine (80-90 days old, weighing 44-54 kg, 12 [Male (M), Female (F)] test, 1 [M] control) were dosed intramuscularly (cervical neck region) with 20 mg ^{14}C-florfenicol/kg on study Day 0 (right side), then 48 hours later on study Day 2 (left side). ^{14}C-Florfenicol was universally labeled in the benzene ring. At 3 days, 6 days, 9 days, and 12 days post-final dose, pigs were slaughtered, and liver, kidneys, muscle, peritoneal fat, and injection site muscle were collected. The control male was not treated and was slaughtered prior to the slaughtering of the test swine. Tissues were analyzed for total radioactivity by combustion and liquid scintillation analysis. Liver samples also were analyzed for florfenicol amine by the HPLC assay. Most of the radioactivity was excreted in the urine (46%-62%) and feces (8%-14%). At the last sampling time point (day 12), the highest concentrations of ^{14}C-florfenicol equivalent residues were found in the liver. The residue present in liver and kidney was predominantly non-extractable residue from which florfenicol amine was

released by acid hydrolysis. The data in Table IV.1 indicate that total residues in liver deplete more slowly than other tissues and that injection site tissue is not a factor in determining the withdrawal period.

Table IV.1. Mean ^{14}C-SCH 25298 equivalent residue concentrations (ppm) in tissues of swine injected intramuscularly with 20 mg ^{14}C-florfenicol/kg two times (48 hours between injections).

Tissue	3 Days Post-dose	6 Days Post-dose	9 Days Post-dose	12 Days Post-dose
Liver	13.93±1.84	9.5±5.24	5.92±1.87	3.22±0.38
Kidney	5.49±0.31	2.5±0.78	1.79±0.35	1.07±0.08
Muscle	0.53±0.13	0.28±0.16	0.20±0.03	0.14±0.02
Fat	0.52±0.24	0.09±0.02	0.07±0.02	0.04±0.01
Left Injection Site	109.91±72.84	3.31±4.87	0.33±0.13	0.14±0.03
Right Injection Site	43.41±71.18	0.87±0.35	0.16±0.02	0.16±0.02

The methanol extractability of ^{14}C-residues from liver and kidney was 13% and 32%, respectively, in day 3 samples and 7% and 8%, respectively, in day 12 samples. Metabolic profiles (methanol extracts) of male and female liver samples (Day 3) in Table IV.2 indicate that there were no sex-related differences in the metabolism of ^{14}C-florfenicol.

Table IV.2. Percent distribution of ^{14}C-florfenicol and metabolites (total radioactive residues, ppm) in male and female swine liver following intramuscular administration of ^{14}C-florfenicol.

^{14}C-Component Retention Time	Day 3 Male n=1 % Distribution/ppm	Day 3 Female n=1 % Distribution/ppm
FFC Oxamic Acid (16 min)	0.0/0.0	1.036/0.1629
Florfenicol Alcohol (18.8 min)	9.849/1.548	7.224/1.136
Unknown #7 (23.2 min)	0.0/0.0	1.56/0.2452
Florfenicol (30 min)	5.1/0.802	3.25/0.5109

Table IV.3 shows the metabolite distribution of radiolabeled components in liver and kidney tissues as determined by reverse phase chromatography.

Table IV.3. Percent distribution of ^{14}C-florfenicol and metabolites (total radioactive residues, ppm) in male and female swine liver and kidney following intramuscular administration of ^{14}C-florfenicol. Data represent pooled samples.

^{14}C-Component Retention Time	**Day 3 Liver/Kidney**	**Day 6 Liver/Kidney**	**Day 9 Liver/Kidney**	**Day 12 Liver/Kidney**
Unknown 1 (3.8 min)	Not detected/ Not detected	Not detected/ 3.4	Not detected/ Not applicable	Not detected/ Not applicable
Unknown 2 (11.1 min)	Not detected/ 2.3	Not detected/ Not detected	Not detected/ Not applicable	Not detected/ Not applicable
FFC Amine (13 min)	0.8/ 2.6	Not detected/ Not detected	Not detected/ Not applicable	Not detected/ Not applicable
Unknown 4 (14.3 min)	Not detected/ 2.7	Not detected/ Not detected	Not detected/ Not applicable	Not detected/ Not applicable
FFC Oxamic Acid (16 min)	4.4/ 2.8	2.6/ Not detected	Not detected/ Not applicable	Not detected/ Not applicable
Unknown 5 (16.3 min)	Not detected/ 3.3	Not detected/ 5.8	Not detected/ Not applicable	Not detected/ Not applicable
Unknown 6 (16.8 min)	Not detected/ 3.2	Not detected/ 2.7	Not detected/ Not applicable	Not detected/ Not applicable
Florfenicol Alcohol (20 min)	3.6/ Not detected	2.9/ Not detected	3.9/ Not applicable	4.9/ Not applicable
Unknown 7 (23 min)	Not detected/ Not detected	Not detected/ Not detected	1.1/ Not applicable	2.1/ Not applicable
Monochloro FFC (23.2 min)	Not detected/ Not detected	Not detected/ Not detected	Not detected/ Not applicable	Not detected/ Not applicable
Florfenicol (29 min)	4.2/ 15.1	0.5/ 0.6	Not detected/ Not applicable	Not detected/ Not applicable

The marker residue to total residue ratio in liver was calculated by comparing the HPLC analysis of florfenicol amine to total radioactive residues. Table IV.4 shows that the percentage of marker residue in total residues of liver at time points post-dose.

Table IV.4. Total radioactive residues in liver as determined by combustion and marker residue (florfenicol amine) concentrations as established by the determinative assay (mean ± standard deviation).

Post Final Dose (days)	Total Residue (ppm)	Florfenicol Amine (ppm)	% Marker Residue in Total Residues
3	13.93 ± 1.84	9.09 ± 1.59	65%
6	9.50 ± 5.24	6.01 ± 3.49	63%
9	5.92 ± 1.87	2.93 ± 0.94	49%
12	3.22 ± 0.38	1.67 ± 0.18	52%

b. Total Residue and Metabolism Study for NMP

The total residue and metabolism study for NMP in swine entitled, "Abbreviated Total Residue and Metabolism Study for ^{14}C-N-methylpyrrolidone administered to swine" is described in ANADA 200-117 for OXYSHOT LA (approval date April 13, 1995). The swine received a single intramuscular injection of 41.32 mg ^{14}C-NMP/kg BW. The data indicate that liver is the target tissue for NMP in swine although total residues of NMP in liver and kidney were very similar. At 1 day withdrawal, the NMP total radioactive residue concentrations in all tissues were substantially below their respective S_m values.

Table IV.5. Mean total residues of NMP equivalents (ppm) in tissues of swine administered a single IM injection of 41.32 mg ^{14}C-NMP/kg (mean ± standard deviation).

Withdrawal Period (days)	Muscle	Kidney	Liver	Fat	Injection Site
1	18.30±1.27	26.55±0.21	21.75±3.32	5.20±0.75	15.15±4.17
4	0.39	0.72	0.23	0.29	0.46
21	0.07±0.03	0.05±0.01	0.14±0.01	0.07±0.02	0.07±0.02

Day 3 data are from a dead animal and are not included in the table.

c. Comparative Metabolism Study for Florfenicol

The metabolism study in the toxicological species (the rat) is described in the FOI Summary for the original approval of Nuflor® injectable solution (NADA 141-063, approval date May 31, 1996). The metabolic profile of florfenicol in the rat was qualitatively similar to that observed in swine. The same florfenicol metabolites that were identified in swine tissues were identified in the rat.

d. Comparative Metabolism Study for NMP

The metabolism study for NMP in the toxicological species entitled, "Comparative Metabolism of ^{14}C-N-methylpyrrolidone in Rats." is described in ANADA 200-117 for OXYSHOT LA (approval date April 13, 1995). The metabolites found in rat liver and urine samples also were found in swine tissues.

e. Tissue Residue Depletion Study to Establish Withdrawal Period

Title: SCH 25298 (Florfenicol): A Final Residue Depletion Study in Swine Following Intramuscular Administration of NUFLOR. (Study Number 97009, Report Number P-6777, December 9, 1997)

Study Dates: August 7, 1997, to December 9, 1997

Study Locations: Santa Ysabel, CA, and Winston-Salem, NC

Objective: The objective of this GLP study was to determine the concentrations of the marker residue in the target and edible swine tissues at selected times following two intramuscular injections, 48 hours apart.

Twenty-one healthy, uniform cross-bred swine (mixed sexes), weighing approximately 30-50 kg body weight, were dosed twice intramuscularly in the neck at 15 mg/kg BW florfenicol with Nuflor® injectable solution. There was a 48-hour interval in between doses. The test animals were slaughtered in groups of five at 3, 6, 9, 12 and 15 days post-final dose. Liver samples were collected and analyzed using the HPLC method that was validated for cattle liver.

Table IV.6. Mean concentration (ppm ± standard deviation) of florfenicol amine in liver samples from swine administered two intramuscular injections of florfenicol at 15 mg/kg (2 doses administered 48-hours apart)

Days Post-Dose	Florfenicol Amine (ppm ± standard deviation)
3	5.04±0.14
6	2.64±0.48
9	1.81±0.59
12	1.27±0.16
15	0.65±0.05

The tissue residue depletion data were analyzed using a 99% tolerance limit and 95% confidence. A withdrawal period of 11 days was calculated.

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. 96363) 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 because the method hydrolyzes parent and all metabolites to that compound.

The target tissue for NMP is liver. The marker residue for NMP is parent NMP.

3. Tolerances and R_m

   Tolerances of 2.5 ppm and 0.2 ppm for florfenicol amine in swine liver and muscle, respectively, were established previously (21 CFR 556.283).

   The R_m for carcinogenic residues, established for parent NMP, is 88 ppm in swine liver.

4. Withdrawal Period

   A withdrawal period of 11 days is calculated for florfenicol amine in swine liver. A withdrawal period of 11 days is consistent with the depletion of florfenicol and NMP residues in all edible tissues following treatment with Nuflor®-S.

E. Analytical Method for Residues

Florfenicol

The FOI Summary for the original approval of NADA 141-206, dated September 4, 2002, contains a summary of the determinative and confirmatory procedures for florfenicol amine (marker residue) in the edible tissues (liver, kidney, muscle, skin with attached fat) of swine receiving Nuflor® 2.3% Concentrate Solution.

N-methyl-2-pyrrolidone (NMP)

1. Determinative Procedure

   Homogenized swine liver is fortified with the deuterated internal standard (NMP-D_9) and extracted first with 20 mL methanol and then with 20 mL acetonitrile. The extract is made up to 50 mL with acetonitrile. An aliquot (0.5 mL) of the methanol extract is diluted with 0.5 mL of acetonitrile and analyzed by LC-MS/MS. The following transitions are monitored for quantitation:

   NMP: m/z 100 → m/z 58

   NMP-D_9: m/z 109 → m/z 62

2. Confirmatory Procedure

   The sample extraction and preparation for the confirmatory procedures are identical to the ones for the determinative procedures. NMP is detected by LC-MS/MS. The following NMP-specific ion transitions are monitored to obtain ion ratios, signal to noise ratios and retention times that meet the required acceptability criteria:

   m/z 100 → m/z 58 (reference ion transition)

   m/z 100 → m/z 82

   m/z 100 → m/z 69

3. Availability of the Method

   The animal drug regulations at 21 CFR 500.1410 provide for the incorporation by reference of the validated regulatory method for NMP. To obtain a copy of the analytical method, please submit a Freedom of Information request to: https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm. Alternatively, a copy of the method may be inspected at the Office of the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, (301) 827-6860, between 9 a.m. and 4 p.m., Monday through Friday or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call (202) 741-6030, or go to http://www.archives.gov/federal-register/cfr/ibr-locations.html.

V. USER SAFETY

N-methyl-2-pyrrolidone (NMP), an ingredient in Nuflor®-S, has been reported to cause reproductive and developmental toxicities in laboratory animals following high, repeated exposures, as described in the following documents from FDA and two other regulatory agencies:

1. FDA/CVM: The FOI Summaries for the original approval of NADA 141-063, dated May 31, 1996, and a supplemental approval, dated May 25, 2018.

2. European Chemical Agency (ECHA): How to comply with REACH Restriction 71, guideline for users of NMP (1-methyl-2-pyrrolidone). ECHA Reference #: ECHA-19-H-07-EN July 2019, [https://echa.europa.eu/-/advice-on-how-to-comply-with-nmp-restriction]

3. United States Environmental Protection Agency (U.S. EPA): Risk Evaluation for n-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) (NMP). EPA Document# EPA-740-R1—8009 December 2020, conducted by the Office of Chemical Safety and Pollution Prevention, Office of Pollution Prevention and Toxics (OPPT) [https://www.epa.gov/sites/production/files/2020-12/documents/1_risk_evaluation_for_n-methylpyrrolidone_nmp_casrn_872-50-4.pdf]

Because there is a risk of exposure to NMP via accidental injection or dermal exposure in pregnant women who handle Nuflor®-S, the Agency recommends that pregnant women wear gloves and exercise caution when handling Nuflor®-S, or avoid handling the product.

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

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.

Reproductive and developmental toxicities have been reported in laboratory animals following high, repeated exposures to NMP. Pregnant women should wear gloves and exercise caution or avoid handling this product. 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. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at www.fda.gov/reportanimalae.

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®-S, when used according to the label, is safe and effective for the treatment of swine respiratory disease associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Salmonella* Choleraesuis, *Streptococcus suis*, *Bordetella bronchiseptica*, and *Glaesserella (Haemophilus) parasuis* in swine except for nursing piglets and swine of reproductive age intended for breeding. Additionally, data demonstrate that residues in food products derived from species treated with Nuflor®-S will not represent a public health concern when the product is used according to the label.

A. Marketing Status

This product may be dispensed only by or on the order of a licensed veterinarian (Rx marketing status). This decision was based on the following factors: adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this drug product, and because restricting this drug product to use by or on the order of a licensed veterinarian is critical for assuring the safe and appropriate use of this drug product in animals in order to mitigate the potential for development of bacterial resistance to antimicrobial drugs.

B. Exclusivity

This supplemental approval for Nuflor®-S qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included safety and effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the use of Nuflor®-S for the treatment of swine respiratory disease associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Salmonella* Choleraesuis, *Streptococcus suis*, *Bordetella bronchiseptica*, and *Glaesserella (Haemophilus) parasuis* in swine except for nursing piglets and swine of reproductive age intended for breeding.

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 Green Book Reports in the Animal Drugs @ FDA database.

VII. APPENDIX

Original text:

FDA used the information from these studies, in combination with the ADI and safe concentrations for florfenicol and the S_o and S_m values for NMP, to establish a tolerance of 2.5 ppm of florfenicol amine in swine liver, an R_m of 500 parts per billion of NMP in swine liver, and a tissue withdrawal period of 11 days.

The R_m for parent NMP is 500 ppb.

Revised text (January 3, 2024):

FDA used the information from these studies, in combination with the ADI and safe concentrations for florfenicol and the S_o and S_m values for NMP, to establish a tolerance of 2.5 ppm of florfenicol amine in swine liver, an R_m of 88 ppm of NMP in swine liver, and a tissue withdrawal period of 11 days.

The R_m for carcinogenic residues, established for parent NMP, is 88 ppm in swine liver.