Date of Approval: January 29, 2014

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-246

AQUAFLOR

Florfenicol

Type A medicated article

Freshwater-reared finfish
Freshwater-reared warmwater finfish
Freshwater-reared salmonids
Catfish

"To provide for an increase in the maximum daily dose for freshwater-reared finfish other than freshwater-reared warmwater finfish to provide a dosage range of 10-15 mg/kg body weight/day and to change the conditions of use to permit the use of florfenicol in recirculating aquaculture systems."

Sponsored by:

Intervet Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-246

B. Sponsor

Intervet, Inc.
556 Morris Ave.
Summit, NJ 07901

Drug Labeler Code: 000061

C. Proprietary Name

AQUAFLOR

D. Established Name

Florfenicol

E. Pharmacological Category

Antimicrobial

F. Dosage Form:

Type A medicated article

G. Amount of Active Ingredient

500 g florfenicol/kg (227.27 g/lb)

H. How Supplied

2 kg foil laminate foil pouch (12 x 16 in)

16 kg fiber board drum (8 x 2 kg pouches)

I. Dispensing Status

VFD

J. Dosage Regimen

10–15 mg/kg body weigh/day for 10 consecutive days

K. Route of Administration

Oral

L. Species/Class

Freshwater-reared finfish
Freshwater-reared warmwater finfish
Freshwater-reared salmonids
Catfish

M. Indications

Catfish: For the control of mortality due to enteric septicemia of catfish associated with *Edwardsiella ictaluri*

Freshwater-reared salmonids: For the control of mortality due to coldwater disease associated with *Flavobacterium psychrophilum*

Freshwater-reared salmonids: For the control of mortality due to furunculosis associated with *Aeromonas salmonicida*

Freshwater-reared warmwater finfish: For the control of mortality due to streptococcal septicemia associated with *Streptococcus iniae*

Freshwater-reared finfish: For the control of mortality due to columnaris disease associated with *Flavobacterium columnare*

N. Effects of Supplement

This supplement provides an increase in the maximum daily dose for freshwater-reared finfish other than freshwater-reared warmwater finfish to provide a dosage range of 10-15 mg/kg body weight (BW)/day and to change the conditions of use to permit the use of florfenicol in recirculating aquaculture systems.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved minimum effective dosage. The Freedom of Information (FOI) Summaries for the original approval of NADA 141-246 dated October 24, 2005, and supplemental approvals dated March 19, 2007, October 26, 2007, and April 4, 2012, contain dosage characterization information.

B. Substantial Evidence

The approval changes the conditions of use to permit the use of florfenicol in recirculating aquaculture systems. This change does not impact Effectiveness. CVM did not require effectiveness studies for this supplemental approval. The FOI Summaries for the original approval of NADA 141-246 dated October 24, 2005, and supplemental approvals March 19, 2007, October 26, 2007, and April 4, 2012, contain summaries of studies that demonstrate effectiveness of the drug for the species, dosage, and indications.

III. TARGET ANIMAL SAFETY:

The approval changes the conditions of use to permit the use of florfenicol in recirculating aquaculture systems. This change does not impact Target Animal Safety. CVM did not require target animal safety studies for this supplemental approval. The FOI Summaries for the original approval of NADA 141-246 dated October 24, 2005, and supplemental approvals dated March 19, 2007, October 26, 2007, and April 4, 2012, contain summaries of target animal safety studies that demonstrate the safety of florfenicol when administered to freshwater-reared finfish at a dosage up to 15 mg florfenicol/kg BW/day for 10 consecutive days.

IV. HUMAN FOOD SAFETY:

A. Antimicrobial Resistance

Due to a low risk of exposure to zoonotic bacterial pathogens, and low risk of severe human disease following consumption of saltwater-reared finfish, the overall microbial food safety (antimicrobial resistance) risk from florfenicol-treated, saltwater-reared finfish is approximately equal to that of florfenicol-treated, freshwater-reared finfish.

Based on recent published literature and information provided in the file, we conclude that an *overall risk estimation* of medium for the proposed use of AQUAFLOR in all finfish to control mortality due to coldwater disease associated with *Flavobacterium psychrophilum*, furunculosis associated with *Aeromonas salmonicida*, enteric septicemia associated with *Edwardsiella ictaluri*, streptococcal septicemia associated with *Streptococcus iniae*, and columnaris disease associated with *Flavobacterium columnare* is appropriate.

Decision Statement:

At this time, no additional risk management steps are required for the proposed use of AQUAFLOR in all finfish beyond those already in place, which include a low to medium extent of use in a targeted group of freshwater- or saltwater-reared finfish, and veterinary oversight of prescription and medication *via* a veterinary feed directive (VFD).

B. Impact of Residues on Human Intestinal Flora:

A microbiological acceptable daily intake (mADI) was previously established for florfenicol, calculated to be 31 micrograms/kg BW/day, or 1.9 mg/person/day.

Decision Statement:

Because the toxicological ADI (tADI) of 10 micrograms/kg BW/day is less than the calculated mADI of 31 micrograms/kg BW/day, the tADI remains the final ADI for total florfenicol residues.

C. Toxicology:

CVM did not require toxicology studies for this supplemental approval. As described in the FOI Summary for the original approval of NADA 141-246 dated October 24, 2005, a summary of all toxicology studies are contained in the FOI Summary for the original approval of NADA 141-063, NUFLOR injectable solution for cattle, dated May 31, 1996.

D. Assignment of the Final ADI:

Because the toxicological ADI of 10 micrograms *per* kilogram of bodyweight *per* day is lower than the calculated microbiological ADI of 31 micrograms *per* kilogram of bodyweight *per* day, the toxicological ADI (10 micrograms/kg BW/day) remains the final ADI for total florfenicol residues.

E. Safe Concentrations for Total Residues (edible tissues and injection sites, if applicable):

No reassessment of the safe concentrations for total residues was needed for this supplemental approval because the final ADI is not changed. The FOI Summary for the original approval of NADA 141-063, NUFLOR injectable solution for cattle, dated May 31, 1996, contains a summary of all toxicology studies. The FOI Summary for the original approval of NADA 141-246 dated October 24, 2005, and the FOI Summary for the supplemental approval of NADA 141-246 dated April 4, 2012, contain an assessment of the impact of residues on human intestinal flora.

F. Residue Chemistry:

1. Summary of Residue Chemistry Studies

a. Total Residue and Metabolism Study

CVM did not require a total residue and metabolism study for this supplemental approval. The FOI Summary for the original approval of NADA 141-246 dated October 24, 2005, contains a summary of the total residue and metabolism study completed in salmonids.

b. Comparative Metabolism Study

Comparative metabolism of florfenicol in the rat (the animal used in the toxicity tests) and in salmon was satisfactorily demonstrated by data in the original approval of NADA 141-063 (florfenicol in cattle, FOI Summary dated May 31, 1996) and in studies conducted in salmonids (FOI Summary for the original approval of NADA 141-246 dated October 24, 2005). In addition, the determinative assay for residues uses an acid-catalyzed hydrolysis step to convert parent florfenicol and florfenicol metabolites to a common marker, florfenicol amine.

c. Tissue Residue Depletion Study

Depletion of florfenicol amine from the fillet tissue of rainbow trout (*Oncorhynchus mykiss*) maintained in recirculating and flow-through aquaculture systems and treated with Aquaflor®-medicated feed (Study Number AEH-11-FFC-01).

Only the residue data from the fish held in the flow-through system are described here because the data from the fish held in the recirculating aquaculture system were not used to support this supplemental approval.

Study Director: Jeffery R. Meinertz, USGS, Upper Midwest Environmental Sciences Center, 2630 Fanta Reed Rd, La Crosse, WI 54603

Study Dates: November 7, 2011 to February 2, 2012

In-Life Facility - Upper Midwest Environmental Sciences Center, 2630 Fanta Reed Rd, La Crosse, WI 54603

Tissue Analytical Facility - MPI Research Inc., State College, PA

One hundred fifty rainbow trout (*Oncorhynchus mykiss*) were held in a flow-through system consisting of one 700-liter circular tank. The temperature of the water flowing through the system was approximately 13°C. The fish were fed feed containing florfenicol at 20 mg/kg bodyweight/day for 10 days (at 1% of total bodyweight in the tank). Five control fish were sampled 5 days prior to the treatment period. After treatment, 16 fish were sampled at 6, 12, 24, 48, 72, 120, 240, 360, and 480 hours postdose. The fish averaged 346 grams body weight (range 126-617 grams). Skin-on fillet tissue was collected from each fish and analyzed for florfenicol amine with the Schering-Plough method titled, "Determination of Florfenicol Amine Residues in Aquaculture Species by HPLC with UV Detection (v. 2.0)". The data demonstrate that florfenicol amine residues deplete to below the 1 ppm tolerance after a withdrawal period of 7 days using 99% statistical tolerance and 95% confidence limits. The withdrawal period also was calculated using only residue data from fish weighing greater than 300 grams to exclude fish that were not market size. A 6-day withdrawal period was calculated for fish weighing greater than 300 grams.

Table 1. Concentration of florfenicol amine (ppm) in muscle/skin of rainbow trout (n=16) treated with florfenicol at a nominal 20 mg/kg body weight/day for 10 days at 13°C.

Withdrawal Period (hours)	Florfenicol amine (ppm)
6	11.09 ± 2.5
12	11.02 ± 2.6
24	7.22 ± 3.6
48	2.54 ± 1.2
72	1.21± 0.39
120	0.49 ± 0.28
240	0.26 ± 0.09
360	0.16 ± 0.05
480	0.11 ± 0.03

LOQ = 0.073 ppm

Public Literature Reference for Florfenicol Residue Data in Fish

The FOI summary for NADA 141-246 (April 4, 2012) included seven public literature references that provide supporting information about the residue depletion of florfenicol in fish species in various water temperatures and housing conditions. The additional public literature reference cited here provides depletion data in two fish species at two water temperatures (13.5°C and 27.4°C) and two housing conditions (flow-through and recirculating tanks).

Di Salvo A, *et al*. 2013. Florfenicol depletion in edible tissue of rainbow trout, *Oncorhynchus mykiss* (Walbaum), and sea bream, *Sparus aurata* L. *Journal of Fish Disease* 38(6):685-693.

Table 2. Florfenicol amine concentrations (ppm) in muscle/skin of trout and sea bream fed medicated feed containing 10 mg florfenicol/kg bw/day for 10 days

Sampling Timepoint	Trout (13.5°C in flow-through tanks)	Sea bream (27.4°C in recirculating tanks)
6 hours	4.08±1.3	---
1 day	2.72±0.6	1.58±0.4
2 days	0.85±0.4	0.81±0.2
3 days	0.51±0.1	0.65±0.3
4 days	0.35±0.1	0.37±0.1
6 days	0.29±0.1	0.28±0.1
7 days	0.28±0.1	0.27±0.5
10 days	<LOQ	All samples <LOQ except one at 0.29
14 days	--	<LOQ

LOQ = 0.25 ppm

2. Target Tissue and Marker Residue

   For fish, the target tissue is muscle with adhering skin except for species such as catfish where the skin is not typically consumed by humans.

   Florfenicol amine is assigned as the marker residue because the determinative method converts parent and all metabolites to that compound.

3. Tolerance Assignment

   The tolerance for florfenicol amine is 1 ppm as described in the original approval of NADA 141-246 dated October 24, 2005.

4. Withdrawal Period

   A 15-day withdrawal period is assigned for freshwater-reared finfish.

G. Analytical Method for Residues:

1. Description of Analytical Method

   The FOI Summary for the original approval of NADA 141-246 dated October 24, 2005, contains the analytical method summaries for florfenicol in catfish. The FOI Summary for the supplemental approval of NADA 141-246 dated March 19, 2007, contains the analytical method summaries for florfenicol in salmonids. The HPLC-UV analytical assays for florfenicol in catfish and salmonids have been combined into one procedure that also includes tilapia.

2. Availability of the Method

   The validated regulatory method for detection and confirmation of residues of florfenicol is available from the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

V. USER SAFETY:

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

"Avoid inhalation, oral exposure, and direct contact with skin or eyes. Operators mixing and handling AQUAFLOR (florfenicol) should use protective clothing, gloves, goggles and NIOSH-approved dust mask. Wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse thoroughly with water. If irritation persists, seek medical attention. Not for human consumption. Keep out of reach of children. The Material Safety Data Sheet (MSDS) contains more detailed occupational safety information. For more information or to report adverse effects, call 1-800-224-5318. For customer service, call 1-800-521-5767. For a copy of MSDS sheet, call 1-800-770-8878."

CVM examined the material safety data sheet to conclude that user safety concerns have been appropriately addressed in the labeling.

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 and 21 CFR part 514. The data demonstrate that AQUAFLOR, when used according to the label, is safe and effective. Additionally, data demonstrate that residues in food products derived from species treated with AQUAFLOR will not represent a public health concern when the product is used according to the label.

A. Marketing Status:

A valid veterinary feed directive (VFD) is required to dispense this drug. Any animal feed bearing or containing this drug will be fed to animals only by or on a lawful veterinary feed directive issued by a licensed veterinarian in the course of their professional practice. In addition, the veterinary feed directives issued for this drug are not refillable.

Labeling restricts this drug to use by or on the order of a licensed veterinarian. The decision to restrict this drug to use by or on the order of a licensed veterinarian was based on the following factors: (a) adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this product and (b) restricting this drug to use by or on the order of a licensed veterinarian should help prevent indiscriminate use which could result in violative tissue residues. Because the drug will be administered in feed, the drug will be marketed as a VFD drug.

B. Exclusivity:

This supplemental approval for AQUAFLOR qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act because the supplemental application included a residue depletion study for a minor species. This exclusivity begins as of the date of this letter/our approval letter and only applies to the increase in the maximum daily dose for freshwater-reared finfish other than freshwater-reared warmwater finfish that is approved in the supplemental application.

C. Supplemental Applications:

This supplemental NADA required/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.