Date of Approval: April 10, 2023

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 038-439

Terramycin® 200 for Fish

(oxytetracycline)

Type A medicated article to be used in the manufacture of Type C medicated feeds

Catfish and freshwater-reared salmonids

This supplement provides for the addition of an indication for the control of mortality due to columnaris disease associated with *Flavobacterium columnare* in catfish and freshwater-reared salmonids.

Sponsored by:

Phibro Animal Health Corp.

Executive Summary

Terramycin® 200 for Fish (oxytetracycline) is approved for the control of mortality due to columnaris disease associated with *Flavobacterium columnare* in catfish and freshwater-reared salmonids. The drug is a Type A medicated article used in the manufacture of a Type C medicated feed containing oxytetracycline, which is an antimicrobial.

Along with other approved uses, Terramycin® 200 for Fish is already approved to control mortality in *Oncorhynchus mykiss* due to columnaris disease associated with *Flavobacterium columnare. Oncorhynchus mykiss* is a type of freshwater-reared salmonid commonly called rainbow trout. This supplemental approval expands the previous approval to include catfish and all freshwater-reared salmonids.

A valid veterinary feed directive (VFD) is required to dispense Type C medicated feed manufactured from Terramycin® 200 for Fish Type A medicated article. The medicated feed can be fed to catfish and freshwater-reared salmonids only by or on a lawful VFD issued by a licensed veterinarian in the course of the veterinarian's professional practice. A VFD issued for a Type C medicated feed containing Terramycin® 200 for Fish cannot be refilled.

Safety and Effectiveness

The sponsor conducted a clinical field study to show that Terramycin® 200 for Fish is effective at controlling mortality in fingerling channel catfish. Fish in the treatment group were fed a Type C medicated feed manufactured from Terramycin® 200 for Fish Type A medicated article, while those in the control group were fed a non-medicated feed for 10 consecutive days. Fish were monitored for mortality during the 10-day treatment period and a 14-day post-treatment period. Columnaris disease was confirmed in the test fish population by using polymerase chain reaction to identify isolates of *Flavobacterium columnare*, the bacterial agent that causes the disease. At the end of the study (Day 24), fish in the treatment group had a reduced mean cumulative mortality compared to fish in the control group. No adverse reactions were reported in the study.

FDA did not require the sponsor to conduct target animal safety studies for this supplemental approval. The original approval of oxytetracycline in fish under this application (NADA 038-439), published in a FEDERAL REGISTER Notice on September 23, 1970, addressed target animal safety in catfish and salmonids. Also, the same dosage is already approved for other indications in these fish species.

Human Food Safety

FDA evaluated the microbial food safety of Terramycin® 200 for Fish for this supplemental approval using a qualitative risk assessment that described oxytetracycline's antimicrobial characteristics with respect to (1) promoting the emergence or selection of antimicrobial resistant bacteria of public health in or on treated catfish and freshwater-reared salmonids; (2) the relative consumption quantities and bacterial contamination rates for food commodities derived from treated catfish and freshwater-reared salmonids; and (3) its importance in human clinical medicine. Results from these components were integrated into an overall risk estimation of medium for the use of Terramycin® 200 for Fish to control columnaris disease in catfish and freshwater-reared salmonids. The risk estimation of medium is

compatible with the Agency's recommended risk management strategies, which include the VFD marketing status.

FDA did not require the sponsor to reassess the acceptable daily intake (ADI) or safe concentration for this supplemental approval. FDA previously established an ADI for total tetracycline residues (chlortetracycline, oxytetracycline, and tetracycline) as 25 µg/kg of body weight per day and the safe concentration for total tetracycline residues in the muscle (with adhering skin) of fish as 2 parts per million. This value reflects the partition of the 60% of the ADI to meat. The Freedom of Information (FOI) Summary for the supplemental approval of another oxytetracycline product for cattle and swine under a different application (NADA 113-232), dated March 28, 1996, and a previous supplemental approval of Terramycin® 200 for Fish, dated June 30, 2006, contain summaries of toxicological studies.

FDA did not require the sponsor to conduct residue chemistry studies for this supplemental approval. The original approval of oxytetracycline in fish under NADA 038-439, dated September 23, 1970, and the FOI Summary for a previous supplemental approval, dated July 6, 2008, contain summaries of residue chemistry studies. This current supplemental approval does not change the previously established withdrawal period of 21 days.

FDA determined that there is a reasonable certainty of no harm for residues of oxytetracycline in the edible tissues of treated catfish and freshwater-reared salmonids following human consumption when Terramycin® 200 for Fish is used according to the labeling.

Conclusions
Based on the data submitted by the sponsor for the approval of Terramycin® 200 for Fish, FDA determined that the drug is safe and effective when used according to the labeling.

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I. GENERAL INFORMATION

A. File Number

NADA 038-439

B. Sponsor

Phibro Animal Health Corp.
GlenPointe Centre East, 3d floor
300 Frank W. Burr Blvd., suite 21
Teaneck, NJ 07666

Drug Labeler Code: 066104

C. Proprietary Name

Terramycin® 200 for Fish

D. Drug Product Established Name

oxytetracycline

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Type A medicated article to be used in the manufacture of Type C medicated feeds

G. Amount of Active Ingredient[1]

200 g/lb

H. How Supplied

50 lb bag

I. Dispensing Status

Veterinary feed directive (VFD)

J. Dosage Regimen

Catfish and freshwater-reared salmonids: 3.75 g oxytetracycline/100 lb of fish/day for 10 days

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[1] The sponsor of this individual currently marketed Type A medicated article may have approvals for other strengths that are for use in the same species and class, for the same indications, and at the same dosages, but are not currently marketing those strengths of this Type A medicated article. Such strengths, when legally marketed, are also approved for use in the manufacture of Type C medicated feeds that are the subject of this approval.

K. Route of Administration

Oral

L. Species/Class

Catfish and freshwater-reared salmonids

M. Indication

For the control of mortality due to columnaris disease associated with *Flavobacterium columnare*.

N. Effect of Supplement

This supplement provides for the addition of an indication for the control of mortality due to columnaris disease associated with *Flavobacterium columnare* in catfish and freshwater-reared salmonids.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage range.

B. Substantial Evidence

1. The FOI Summary for the supplemental approval of NADA 038-439 dated July 6, 2008, contains a summary of studies that demonstrate effectiveness of the drug for the control of mortality in *Oncorhynchus mykiss* due to columnaris disease associated with *Flavobacterium columnare*.

2. Clinical Field Study

   Title: The Efficacy of Terramycin® 200 for Fish (Oxytetracycline Dihydrate)-Medicated Feed to Control Mortality in Fingerling Channel Catfish *Ictalurus punctatus* Caused by Columnaris Disease *Flavobacterium columnare*. (Study No. OTC-10-EFF-03)

   Study Dates: September 2018 to April 2019

   Study Location: Webster, Florida

   Study Design:

   Objective: To evaluate the effectiveness of Terramycin® 200 for Fish (oxytetracycline) Type A medicated article to control mortality in fingerling channel catfish *Ictalurus punctatus* due to columnaris disease associated with *Flavobacterium columnare*.

   Study Animals: Approximately 15,200 fingerling channel catfish, mean length 6.43 cm, mean weight 5.5 g.

Experimental Design: A completely randomized design was used to equally divide fish from the reference population into two treatment groups: 1) a control group which received unmedicated feed; and 2) a treated group which received Terramycin® 200 for Fish (oxytetracycline) Type A medicated article. There were four tanks in each treatment group and each tank contained approximately 1,900 fish. Study personnel responsible for collecting data were masked to treatment assignments. The study was conducted according to Good Clinical Practice (GCP) standards.

Drug Administration: Fish in treated tanks were fed at a rate of 3.75 g oxytetracycline/100 lbs of fish/day for 10 consecutive days. Fish in control tanks received only unmedicated feed of the same size and nutrient composition.

Measurements and Observations: Presumptive diagnosis of columnaris disease associated with *Flavobacterium columnare* was based on skin and gill wet mounts and posterior kidney cultures; and identification of bacterial isolates was confirmed by Polymerase Chain Reaction (PCR) specific to *Flavobacterium columnare*. Mortality was the primary variable and was recorded daily during the 10-day treatment period and 14-day post-treatment period. Multiple feed samples were collected from the medicated and unmedicated feeds. The feeds were analyzed for oxytetracycline concentration. Dissolved oxygen and temperature were recorded daily for each test tank during the treatment period. Water hardness was recorded once in one treated tank, and total alkalinity and pH were recorded once in the reference population tank and one treated tank.

Statistical Methods: The proportion of cumulative mortality was analyzed using a generalized linear mixed model with a logit link. The model included treatment as a fixed effect and the random effect of tank was modeled with a R-side covariance structure. The difference between the treated and control groups with respect to cumulative mortality was tested using a two-sided alpha = 0.05.

Results: Columnaris disease was confirmed in the test fish population by positive PCR results for the causative agent, *Flavobacterium columnare*.

The mean cumulative mortality at the end of the study (day 24) in the treated group (0.81%) was significantly different (P = 0.0058) from that in the control group (2.39%).

Results for the feed analysis showed that the drug administration was appropriate to achieve a rate of 3.75 g oxytetracycline/100 lbs of fish/day. Temperature and dissolved oxygen were consistent throughout the study for all test tanks, and mean values across all test tanks were 23.8˚C and 12.7 mg/L, respectively. Mean water alkalinity and hardness values (as $CaCO_3$) were 288.5 mg/L and 209 mg/L, respectively, and mean pH was 7.63.

Adverse Reactions: No adverse reactions were reported in this study.

Conclusion: This study demonstrated the effectiveness of Terramycin® 200 for Fish (oxytetracycline) Type A medicated article administered at a rate of 3.75 g oxytetracycline/100 lbs of fish/day for 10 consecutive days to control

mortality in fingerling channel catfish *Ictalurus punctatus* due to columnaris disease associated with *Flavobacterium columnare.*

III. TARGET ANIMAL SAFETY

CVM did not require additional target animal safety studies for catfish or salmonids for this approval. A FEDERAL REGISTER Notice for the original approval of NADA 038-439 published on September 23, 1970, and this dosage has been codified in 21 CFR 558.450(e)(5)(iv) for other indications for catfish and salmonids.

IV. HUMAN FOOD SAFETY

A. Microbial Food Safety

Background and outcome of risk assessment.

Microbial food safety (antimicrobial resistance) information for oxytetracycline dihydrate for the proposed supplement to NADA 038-439 was evaluated using a qualitative risk assessment approach. This supplemental approval is for the control of mortality due to columnaris disease associated with *Flavobacterium columnare* in catfish and freshwater-reared salmonids (except *Oncorhynchus mykiss*). Microbial food safety information for the use in *Oncorhynchus mykiss* was previously assessed (refer to the FOI summary for NADA 038-439 dated July 6, 2008).

The qualitative microbial food safety risk assessment for this supplemental approval included: 1) a *release assessment* to describe the probability that use of oxytetracycline dihydrate in freshwater-reared salmonids and catfish will result in the emergence of antimicrobial drug-resistant bacteria of public health concern; 2) an *exposure assessment* to describe the likelihood of human exposure to such resistant bacteria through consumption of edible products from treated catfish and freshwater-reared salmonids (except *Oncorhynchus mykiss*); and 3) a *consequence assessment* to describe potential human health consequences arising from exposure to defined resistant bacteria by considering the human medical importance of tetracyclines used for treatment of human infectious diseases.

Based upon the Agency's evaluation, and in consideration of the impact from the relatively small additional quantity of oxytetracycline dihydrate used as a result of this supplement approval, and a low relevance of tetracycline use in human medicine for treating illnesses attributable to pathogens associated with aquatic species, it is reasonably determined that the overall risk estimation associated with the use of this product under newly proposed conditions of use is **medium**, integrated from individual rankings of high for the *release assessment*, low for the *exposure assessment*, and medium for the *consequence assessment*. This risk estimation is compatible with recommended Agency risk management strategies, which includes VFD marketing status.

Decision Statement:

The Agency's risk estimation of **medium** is compatible with proposed conditions of use and recommended risk management strategies for this supplemental

application for the use of oxytetracycline in catfish and freshwater-reared salmonids (except *Oncorhynchus mykiss*).

B. Toxicology

Reassessment of the codified ADI or safe concentration was not needed for this supplemental approval. The codified ADI for total tetracycline residues (chlortetracycline, oxytetracycline, and tetracycline) is 25 µg/kg bw/day as listed under 21 CFR §556.500. The safe concentration for total tetracycline residues (tetracycline, chlortetracycline, and oxytetracycline) in the muscle (with adhering skin) of fish is 2 ppm. This value reflects the partition of the 60% of the ADI to meat. The FOI Summaries for the supplemental approval of NADA 113-232, dated March 28, 1996, and the supplemental approval of NADA 038-439, dated June 30, 2006, contain a toxicology summary.

C. Residue Chemistry

CVM did not require residue chemistry studies for this supplemental approval. The original approval of NADA 038-439 (48 FR 14759, September 23, 1970) and the FOI summary for the supplemental approval dated July 6, 2008, contain summaries of residue chemistry studies.

This supplement does not result in any change to the previously established withdrawal period. The withdrawal period remains 21 days (21 CFR §558.450).

D. Analytical Method for Residues

1. Description of Analytical Method

   The analytical method for detection of oxytetracycline is a microbiological assay using *Bacillus cereus* var. *mycoides*. This method may be found in "Antibiotic Residues in Milk, Dairy Products, and Animal Tissues: Methods, Reports, and Protocols" (revised October 1968, reprinted December 1974), National Center for Antibiotic and Insulin Analysis, FDA, Washington, DC 20204.

2. Availability of the Method

   The validated analytical method for analysis of residues of oxytetracycline 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 request to: https://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Terramycin® 200 for Fish:

Certain components of animal feeds, including medicated articles, possess properties that may be a potential health hazard or a source of personal discomfort to certain individuals who are exposed to them. Human exposure should, therefore, be minimized by observing the general industry standards for occupational health and safety.

Precautions such as the following should be considered: dust masks or respirators and protective clothing should be worn; dust-arresting equipment and adequate ventilation should be utilized; personal hygiene should be observed; wash before eating or leaving a work site; be alert for signs of allergic reactions—seek prompt medical treatment if such reactions are suspected.

NOT FOR HUMAN USE

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 Terramycin® 200 for Fish, when used according to the label, is safe and effective for the control of mortality due to columnaris disease associated with *Flavobacterium columnare* in catfish and freshwater-reared salmonids. Additionally, data demonstrate that residues in food products derived from species treated with Terramycin® 200 for Fish will not represent a public health concern when the product is used according to the label.

A. Marketing Status

A valid 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.

The decision to restrict this drug to use by or upon a lawful veterinary feed directive issued by a licensed veterinarian was based on the following factors: adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this drug product, 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, and to ensure that edible tissue derived from animals treated with this drug product is safe with regards to human consumption.

B. Exclusivity

This supplemental approval for Terramycin® 200 for Fish qualifies for SEVEN years of exclusive marketing rights beginning as of the date of our approval letter. This drug qualifies for exclusive marketing rights under section 573(c) of the FD&C Act because it is a designated new animal drug under section 573(a) of the FD&C Act. Except as provided in section 573(c)(2) of the FD&C Act, we may not approve or conditionally approve another application submitted for such new animal drug with the same intended use as Terramycin® 200 for Fish. Terramycin® 200 for Fish as approved in our approval letter, does not qualify for marketing exclusivity under section 512(c)(2)(F) of the FD&C Act.

Note that the SEVEN years of exclusive marketing rights granted for the control of mortality in catfish and freshwater-reared salmonids due to columnaris disease associated with *Flavobacterium columnare* applies for catfish and freshwater-

reared salmonids except *Oncorhynchus mykiss*. Approval for this indication for *Oncorhynchus mykiss* was granted in the supplemental approval of NADA 038-439 dated July 6, 2008, and seven years exclusive marketing rights for that indication began on that date.

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.