Date of Approval: May 31, 2018

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-495

Inteprity™ and Bio-Cox®

(avilamycin Type A medicated article and salinomycin sodium Type A medicated article)

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

Broiler chickens

Original approval of an Animal Drug Availability Act (ADAA) of 1996 feed combination for the indications listed in Section I.L.

Sponsored by:

Elanco US Inc.

TABLE OF CONTENTS

I. GENERAL INFORMATION

A. File Number

NADA 141-495

B. Sponsor

Elanco US Inc.
2500 Innovation Way
Greenfield, IN 46140

Drug Labeler Code: 058198

C. Proprietary Names

Inteprity™ and Bio-Cox®

D. Product Established Names

avilamycin Type A medicated article and salinomycin sodium Type A medicated article

E. Pharmacological Categories

Inteprity™: antimicrobial
Bio-Cox®: anticoccidial

F. Dosage Form

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

G. Amount of Active Ingredients in Currently Marketed Products[1]

Inteprity™: 45.4 g/lb avilamycin
Bio-Cox®: 60 g/lb of salinomycin sodium activity

H. How Supplied

Inteprity™ (avilamycin Type A medicated article): 25 kg bag (55.12 lb bag)
Bio-Cox® (salinomycin sodium Type A medicated article): 50 lb bag

I. Dispensing Status

VFD

[1] The sponsors of these individual currently marketed Type A medicated articles 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 these Type A medicated articles. 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.

J. Route of Administration

Oral

K. Species/Class

Broiler chickens

L. Indication(s) and Dosage Regimen(s)

For the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens*; and for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. brunetti,* and *E. mivati* in broiler chickens.

a. 13.6 to 40.9 g/ton of Inteprity™ for the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens* in broiler chickens.

b. 40 to 60 g/ton of Bio-Cox® for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. brunetti,* and *E. mivati* in broiler chickens.

Feed as the sole ration for 21 consecutive days.

II. EFFECTIVENESS

In accordance with the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the ADAA of 1996, if the animal drugs or active ingredients intended for use in combination in an animal feed have already been separately approved for the particular uses and conditions for which they are intended for use in combination, the Center for Veterinary Medicine (CVM) will not refuse to approve an NADA for the combination on effectiveness grounds unless the FDA finds that the sponsor fails to demonstrate that:

- there is substantial evidence to indicate that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the proposed combination makes a contribution to the labeled effectiveness
- each of the active ingredients or animal drugs intended for at least one use that is different from all other active ingredients or animal drugs used in the combination provides appropriate concurrent use for the intended target population
- where the combination contains more than one nontopical antibacterial active ingredient or animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients or animal drugs makes a contribution to the labeled effectiveness.

Inteprity™, as provided by Elanco US Inc., has previously been separately approved for use in feed for broiler chickens for the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens* (21 CFR 558.68). Bio-Cox®, as provided by Huvepharma EOOD, has previously been separately approved for use in feed for broiler chickens for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. brunetti,* and *E. mivati* (21 CFR 558.550).

Effectiveness of each drug, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Huvepharma EOOD's approved NADA 128-686 for Bio-Cox®, to which Elanco US Inc. has right of reference, and in Elanco US Inc.'s approved NADA 141-439 for Inteprity™, respectively.

Because Inteprity™ and Bio-Cox® each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that Inteprity™ plus Bio-Cox® provide appropriate concurrent use for the intended target population. The use of Inteprity™ plus Bio-Cox® provides appropriate concurrent use because these drugs are intended to treat different conditions (necrotic enteritis and coccidiosis, respectively) likely to occur simultaneously with sufficient frequency in broiler chickens. There is no more than one nontopical antibacterial contained in this combination animal drug intended for use in Type C medicated feed.

III. TARGET ANIMAL SAFETY

In accordance with the FD&C Act, as amended by the ADAA of 1996, if the animal drugs or active ingredients intended for use in combination in animal feed have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, CVM will not refuse to approve an NADA for the combination on target animal safety grounds unless:

- there is a substantiated scientific issue specific to an active ingredient or animal drug used in the combination that cannot adequately be evaluated based on the information contained in the application for the combination, and CVM finds that the application fails to show that the combination is safe, or
- there is a scientific issue raised by target animal observations contained in the studies submitted to the NADA for the combination, and CVM finds that the application fails to show that the combination is safe.

Inteprity™, as provided by Elanco US Inc., has previously been separately approved for use in feed for broiler chickens for the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens* (21 CFR 558.68). Bio-Cox®, as provided by Huvepharma EOOD, has previously been separately approved for use in feed for broiler chickens for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. brunetti,* and *E. mivati* (21 CFR 558.550).

Under the provisions of ADAA, this original approval allows for the combination of Inteprity™ and Bio-Cox®. Target animal safety for each drug, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Huvepharma EOOD's approved NADA 128-686 for Bio-Cox®, to which Elanco US Inc. has right of reference, and in Elanco US Inc.'s approved NADA 141-439 for Inteprity™. The Agency has found no substantiated scientific issue relating to the target animal safety of Inteprity™ and Bio-Cox® when used in combination under this NADA and no scientific issue has been raised by target animal observations submitted as part of the NADA for this combination. Therefore, in accordance with the FD&C Act, as amended by the ADAA of 1996, no specific target animal safety studies are required for approval of this application.

IV. HUMAN FOOD SAFETY

In accordance with the FD&C Act, as amended by the ADAA of 1996, if the animal drugs or active ingredients intended for use in combination in animal feed have already been separately approved for the particular uses and conditions of use for which they are intended for use in combination, CVM will not refuse to approve an NADA for the combination on human food safety grounds unless CVM finds that the application fails to establish that:

- none of the active ingredients or animal drugs used in combination at the longest withdrawal for any of the active ingredients or animal drugs in the combination exceeds the established tolerance, or
- none of the active ingredients or animal drugs in combination interferes with the method of analysis for another active ingredient or animal drug in the combination.

A. Toxicology

Safety of the individual drugs in this combination product has been established by data in NADA 141-438 for avilamycin (FOI Summary dated May 8, 2015) and NADA 128-686 for salinomycin sodium (FR Vol. 48 No. 129 pg. 30616, dated July 5, 1983).

B. Residue Chemistry

1. Summary of Residue Chemistry Studies

   CVM did not require residue chemistry studies for this approval. Data demonstrated residue depletion and assay noninterference for avilamycin and salinomycin were not required because neither a target tissue nor a marker residue is codified for avilamycin or salinomycin in chickens and neither compound requires a tolerance in chickens.

2. Target Tissue and Marker Residue Assignment

   No reassessments of target tissue and marker residue were needed for this approval. Neither a target tissue nor a marker residue is codified for avilamycin or salinomycin in chickens.

3. Tolerance Assignments

   A tolerance for residues of avilamycin in chickens is not required (21 CFR 556.68). A tolerance for residues of salinomycin in chickens is not required (21 CFR 556.592).

4. Withdrawal Period

   Based on the data summarized in NADA 141-439 and NADA 128-686 for avilamycin and salinomycin sodium, respectively, a 0-day withdrawal is assigned for chickens fed avilamycin at up to 40.9 g/ton of feed and salinomycin sodium at up to 60 g/ton of feed for up to 21 days.

C. Microbial Food Safety

With respect to the human food safety evaluation for these types of combination new animal drug approvals, the Agency is permitted only to evaluate whether any active ingredient or drug intended for use in the combination exceeds its established tolerance at the longest withdrawal time of any of the active ingredients or drugs in the combination, and whether any of the active ingredients or drugs of the combination interferes with the methods of analysis of another active ingredient or drug in the combination [section 512(d)(4)(A) of the Federal Food, Drug, and Cosmetic Act]. Therefore, the effects of this combination of avilamycin and salinomycin sodium on 1) antimicrobial resistance among bacteria of public health concern in or on treated broiler chickens, and 2) the intestinal flora of human consumers of food derived from treated broiler chickens will not be assessed.

D. Analytical Method for Residues

Because a tolerance has not been assigned for either avilamycin or salinomycin, a validated analytical method is not necessary for either drug.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to the Type C medicated feed:

Not for use in humans. Keep out of reach of children.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the FD&C Act and 21 CFR part 514. The data contained in the previously approved NADAs for Inteprity™ and Bio-Cox® demonstrate that, when they are used according to the label, they are safe and effective for the prevention of mortality caused by necrotic enteritis associated with *Clostridium perfringens*; and for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. maxima, E. brunetti,* and *E. mivati* in broiler chickens. Additionally, data demonstrate that residues in food products derived from broiler chickens administered Inteprity™ and Bio-Cox® will not represent a public health concern when the combination medicated feed 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 VFDs issued for this drug are not refillable.

Labeling restricts this drug to use under the professional supervision of a licensed veterinarian. The decision to restrict this drug to use by or upon a lawful VFD issued by a licensed veterinarian was based on the following factors: (a) adequate directions cannot be written to enable lay persons to appropriately and safely use this product and (b) restricting this drug to use by or upon a lawful VFD issued by

a licensed veterinarian should help prevent indiscriminate use, which could result in violative tissue residues.

B. Exclusivity

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(ii) of the FD&C Act.

C. Patent Information

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