

Date of Approval: March 2, 2018

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-484

Bio-Cox® and LINCOMIX®

(salinomycin sodium Type A medicated article and lincomycin
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 and Availability Act (ADAA) of 1996 feed
combination for the indications listed in Section I.L.

Sponsored by:

Zoetis Inc.

TABLE OF CONTENTS

I.	GENERAL INFORMATION.....	3
II.	EFFECTIVENESS	4
III.	TARGET ANIMAL SAFETY	5
IV.	HUMAN FOOD SAFETY	6
	A. Toxicology	6
	B. Residue Chemistry	6
	C. Microbial Food Safety	7
	D. Analytical Method for Residues	8
V.	USER SAFETY.....	8
VI.	AGENCY CONCLUSIONS.....	8
	A. Marketing Status	8
	B. Exclusivity	9
	C. Patent Information.....	9

I. GENERAL INFORMATION

A. File Number

NADA 141-484

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

Bio-Cox[®] and LINCOMIX[®]

D. Product Established Names

salinomycin sodium Type A medicated article and lincomycin Type A medicated article

E. Pharmacological Category

Bio-Cox[®]: anticoccidial
LINCOMIX[®]: antimicrobial

F. Dosage Form

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

G. Amount of Active Ingredient in Currently Marketed Products¹

Bio-Cox[®]: 60 g/lb of salinomycin sodium activity
LINCOMIX[®]: 20 or 50 g/lb of lincomycin (as lincomycin hydrochloride agricultural grade)

H. How Supplied

Bio-Cox[®]: 50 lb bag
LINCOMIX[®]: 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 of these products 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 and Dosage Regimen

For the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. maxima*, *E. brunetti*, and *E. mivati*, and for the control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to lincomycin in broiler chickens.

1. 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*.
2. 2 g/ton of LINCOMIX® for the control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to lincomycin.

Feed as the sole ration to broiler chickens.

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.

Salinomycin sodium Type A medicated article, 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). Lincomycin Type A medicated article, as provided by Zoetis Inc., has previously been separately approved for use in feed for broiler chickens for the control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to lincomycin (21 CFR 558.325).

Effectiveness of each drug, salinomycin sodium Type A medicated article and lincomycin Type A medicated article, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Huvepharma EOOD's NADA 128-686 for salinomycin sodium Type A medicated article to which Zoetis Inc. has right of reference, and in Zoetis Inc.'s approved NADA 097-505 for lincomycin Type A medicated article.

Because salinomycin sodium Type A medicated article and lincomycin Type A medicated article each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that salinomycin sodium Type A medicated article plus lincomycin Type A medicated article provide appropriate concurrent use for the intended target population. The use of salinomycin sodium Type A medicated article plus lincomycin Type A medicated article provides appropriate concurrent use because these drugs are intended to treat different conditions (prevention of coccidiosis and control of necrotic enteritis, 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.

Salinomycin sodium Type A medicated article, 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). Lincomycin Type A medicated article, as provided by Zoetis Inc., has previously been separately approved for use in feed for broiler chickens for the control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to lincomycin (21 CFR 558.325).

Under the provisions of ADAA, this original approval allows for the combination of salinomycin sodium Type A medicated article (as provided by Huvepharma EOOD) and lincomycin Type A medicated article (as provided by Zoetis Inc.). Target animal safety for each drug, salinomycin sodium Type A medicated article and lincomycin Type A medicated article, when administered alone in accordance with its approved uses and conditions of use is demonstrated in Huvepharma EOOD's NADA 128-686 for salinomycin sodium Type A medicated article to which Zoetis Inc. has right of reference, and in Zoetis Inc.'s approved NADA 097-505 for lincomycin Type A

medicated article. The Agency has found no substantiated scientific issue relating to the target animal safety of salinomycin sodium Type A medicated article and lincomycin Type A medicated article 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 128-686 for salinomycin sodium (FR Vol. 48 No. 129 pg. 30616, dated July 5, 1983) and NADA 111-636 for lincomycin (FOI Summary dated January 23, 1990).

B. Residue Chemistry

1. Summary of Residue Chemistry Studies

a. Total Residue and Metabolism Studies

CVM did not require total residue and metabolism studies for this approval. NADA 128-686 contains summaries of studies supporting the approval of salinomycin sodium in broiler chickens (FR Vol. 48 No. 129 pg. 30616, dated July 5, 1983). NADA 097-505 contains summaries of studies supporting the approval of lincomycin in broiler chickens (FR Vol. 35 No. 91 pg. 7300, dated May 9, 1970).

b. Comparative Metabolism Studies

CVM did not require comparative metabolism studies for this approval. NADA 128-686 contains summaries of studies supporting the approval of salinomycin sodium in broiler chickens (FR Vol. 48 No. 129 pg. 30616, dated July 5, 1983). NADA 097-505 contains studies supporting the approval of lincomycin in broiler chickens (FR Vol. 35 No. 91 pg. 7300, dated May 9, 1970).

c. Tissue Residue Depletion Study

Because tolerances are not established in edible chicken tissues for residues of salinomycin sodium (21 CFR 556.592) and lincomycin (21 CFR 556.360),

- (1) the concentrations of salinomycin sodium and lincomycin residues in edible chicken tissues were not evaluated, and
- (2) the effect that lincomycin has on the assay of salinomycin sodium and the effect that salinomycin sodium has on the assay of lincomycin was not evaluated for this ADAA combination approval.

2. Target Tissue and Marker Residue Assignment

A target tissue and marker residue are not assigned for salinomycin in edible chicken tissues (21 CFR 556.592).

A target tissue and marker residue are not assigned for lincomycin in edible chicken tissues (21 CFR 556.360).

3. Tolerance Assignments

A tolerance for residues of salinomycin sodium is not established in edible chicken tissues (FR Vol. 48 No. 129 pg. 30616, dated July 5, 1983; 21 CFR 556.592).

A tolerance for residues of lincomycin is not required in edible chicken tissues (FR Vol. 55 No. 91 pg. 3208, dated January 31, 1990; 21 CFR 556.360).

4. Withdrawal Period

A 0-day withdrawal period is assigned for the combined use of Bio-Cox® and LINCOMIX® when fed to broiler chickens as a Type C medicated feed containing 40 to 60 g/ton salinomycin sodium and 2 g/ton lincomycin.

C. Microbial Food Safety

1. Antimicrobial Resistance

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 FD&C Act]. Therefore, the effect of this combination of salinomycin sodium and lincomycin on antimicrobial resistance among bacteria of public health concern in or on treated broiler chickens was not assessed.

2. Impact of Residues on Human Intestinal Flora

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 FD&C Act]. Therefore, the effect of this combination of salinomycin sodium and lincomycin on the human intestinal flora was not assessed.

D. Analytical Method for Residues

Because tolerances for residues of salinomycin sodium and lincomycin are not established for edible chicken tissues, analytical methods are not required.

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 Bio-Cox[®] and LINCOMIX[®] demonstrate that, when used according to the label, they are safe and effective for the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. maxima*, *E. brunetti*, and *E. mivati*, and for the control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to lincomycin in broiler chickens. Additionally, data demonstrate that residues in food products derived from broiler chickens treated with Bio-Cox[®] and LINCOMIX[®] 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 VFD 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.