Date of Approval: October 15, 2018

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-485

COYDEN® and LINCOMIX®

(clopidol 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 Availability Act of 1996 (ADAA) feed combination for the indication(s) listed in Section I.L.

Sponsored by:

Zoetis Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-485

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Names

COYDEN® and LINCOMIX®

D. Drug Product Established Names

clopidol Type A medicated article and lincomycin Type A medicated article

E. Pharmacological Categories

COYDEN®: 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 Ingredients in Currently Marketed Products[1]

COYDEN®: 113.5 g/lb (25%) clopidol
LINCOMIX®: 20 or 50 g/lb lincomycin (as lincomycin hydrochloride agricultural grade)

H. How Supplied

COYDEN®: 50 lb bag
LINCOMIX®: 50 lb bag

I. Dispensing Status

VFD

J. Route of Administration

Oral

[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.

K. Species/Class

Broiler chickens

L. Indication and Dosage Regimen

1. As an aid in the prevention of cecal and intestinal coccidiosis caused by *E. 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.

    a. 113.5 g/ton of COYDEN® as an aid in the prevention of cecal and intestinal coccidiosis caused by *E. tenella, E. necatrix, E. acervulina, E. maxima, E. brunetti,* and *E. mivati*.

    b. 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 AND TARGET ANIMAL SAFETY

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the ADAA of 1996, allows for drugs to be fed in combination in Type C medicated feeds without additional demonstration of their effectiveness or target animal safety. The FD&C Act reaffirms that effectiveness and target animal safety of each drug were adequately demonstrated in its NADA at the time of the approval. The Agency has based its determination of the effectiveness and target animal safety of the combination of clopidol and lincomycin on the effectiveness and target animal safety of the previously separately approved conditions of use for COYDEN® and LINCOMIX® for use in broiler chickens, respectively, as these drugs or their active ingredients intended for use in combination in animal feeds have met the following criteria:

- 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;
- there was not a substantiated scientific issue specific to an active ingredient or animal drug used in the combination that was not adequately evaluated based on the information contained in the application for the combination, and no data presented in the application raised a safety concern with the Agency; or
- there was not a scientific issue raised by target animal observations contained in the studies submitted to the NADA for the combination, and no data presented in the application raised a safety concern with the Agency.

Effectiveness and target animal safety of the individual drugs in this combination

product have been established by data in the following NADAs (see Table II.1):

Table II.1. Summary of effectiveness and target animal safety for the individual drugs subject to this combination approval.

Drug Product	Information Indication	Approval
COYDEN®* Sponsored by Huvepharma EOOD	For use in feeds for broiler chickens as an aid in the prevention of cecal and intestinal coccidiosis caused by *E. tenella, E. necatrix, E. acervulina, E. maxima, E. brunetti,* and *E. mivati*.	NADA 034-393 (as published in the FEDERAL REGISTER (33 FR 17628) on November 26, 1968)
LINCOMIX® Sponsored by Zoetis Inc.	For use in feeds for broiler chickens for the control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to lincomycin.	NADA 097-505 (as published in the FEDERAL REGISTER (42 FR 37545) on July 22, 1977)

*Huvepharma EOOD has provided Zoetis Inc. right of reference to use COYDEN® in this combination.

III. HUMAN FOOD SAFETY

The FD&C Act, as amended by the ADAA of 1996, allows for drugs to be fed in combination in Type C medicated feeds without additional demonstration of human food safety. The human food safety of each drug was adequately demonstrated in its NADA at the time of the approval. The Agency has based its determination of the human food safety of the combination of clopidol and lincomycin on the human food safety of the previously separately approved conditions of use for COYDEN® and LINCOMIX® for use in broiler chickens, respectively, as these drugs or their active ingredients intended for use in combination in animal feeds have met the following criteria:

- 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 the following NADAs (see Table III.1):

Table III.1. Establishment of the human food safety of individual drugs in this combination product.

Drug Product	Approval Information
clopidol	NADA 034-393 (as published in the FEDERAL REGISTER (33 FR 17627) on November 26, 1968)
lincomycin	NADA 111-636 (refer to the 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 034-393 contains summaries of studies supporting the approval of clopidol in broiler chickens (as published in the FEDERAL REGISTER (33 FR 17627) on November 26, 1968). NADA 097-505 contains summaries of studies supporting the approval of lincomycin in broiler chickens (as published in the FEDERAL REGISTER (35 FR 7300) on May 9, 1970).

   b. Comparative Metabolism Studies

   CVM did not require comparative metabolism studies for this approval. NADA 034-393 contains summaries of studies supporting the approval of clopidol in broiler chickens (as published in the FEDERAL REGISTER (33 FR 17627) on November 26, 1968). NADA 097-505 contains studies supporting the approval of lincomycin in broiler chickens (as published in the FEDERAL REGISTER (35 FR 7300) on May 9, 1970).

   c. Tissue Residue Depletion Study

   For ADAA combination approvals, section 512(d)(4)(A) of the FD&C Act only permits the Agency to evaluate whether any active ingredients or drugs, at the longest withdrawal period for either active ingredient or drug, exceeds its established tolerance. Therefore, because a tolerance for lincomycin is not required in edible chicken tissues (21 CFR 556.360), there is no requirement to assess the effect of clopidol on the depletion or assay of lincomycin residues in edible chicken tissues in support of this approval. The Agency did evaluate a study that assessed the effect of lincomycin on the depletion and assay of clopidol residues in edible tissues of chickens.

   Title: A RESIDUE STUDY: CLOPIDOL IN CHICKEN TISSUES FROM FEED MEDICATED WITH COYDEN® IN COMBINATION WITH LINCOMYCIN AND 3-NITRO OR ARSANILIC ACID

   In-life Animal Phase Study Location: Kalamazoo, MI, USA

Analytical Phase Study Location: Midland, MI, USA

Study Completion Date: January 22, 1969

The objective of this study was to determine the concentration of clopidol residues in edible tissues of chickens fed lincomycin and clopidol.

Four groups of six chickens each (three males, three females *per* group) were used in this study (Table III.2). All groups were fed their respective diets for 56 days. Group 1 chickens were fed unmedicated feed. Group 2 chickens were fed a Type C medicated feed containing 25 g/ton lincomycin. Group 3 chickens were fed a Type C medicated feed containing 25 g/ton lincomycin, 113.4 g/ton clopidol, and 154.2 g/ton arsanilic acid[2]. Group 4 chickens were fed a Type C medicated feed containing 25 g/ton lincomycin, 113.4 g/ton clopidol, and 45.4 g/ton 3-nitro-4-hydroxyphenyl arsenic acid (3-nitro)[3].

Table III.2. Treatment groups and inclusion rates for lincomycin, clopidol, arsanilic acid, and 3-nitro.

Group	Lincomycin Feed Concentration	Clopidol Feed Concentration	Arsanilic Acid Feed Concentration	3-nitro Feed Concentration
1	0 g/ton	0 g/ton	0 g/ton	0 g/ton
2	25 g/ton	0 g/ton	0 g/ton	0 g/ton
3	25 g/ton	113.4 g/ton	154.2 g/ton	0 g/ton
4	25 g/ton	113.4 g/ton	0 g/ton	45.4 g/ton

For analysis of clopidol tissue concentrations, chickens were slaughtered at 0-day withdrawal from medicated feed. Muscle, liver and kidney tissues were collected and analyzed for clopidol concentration by gas chromatography (Table III.3).

[2] Arsanilic acid is not approved by the FDA as a new animal drug product.
[3] Approval of the roxarsone Type A medicated article, 3-Nitro®, has been withdrawn (as published in the FEDERAL REGISTER (78 FR 70062) on November 22, 2013. After evaluation of the tissue residue interference study, it was determined that the data from the study for the three-way combination (lincomycin at 25 g/ton, clopidol at 113.4 g/ton, and roxarsone at 45 g/ton, and lincomycin 1.8 g/ton) could be used to support tissue residue non-interference and a zero-day withdrawal assignment for the two-way combination (113.5 g/ton clopidol and 2 g/ton lincomycin).

Table III.3. Mean (± standard deviation) clopidol concentrations in edible tissues from broiler chickens fed unmedicated feed (Group 1); feed containing lincomycin (Group 2); feed containing lincomycin, clopidol and arsanilic acid (Group 3); or feed containing lincomycin, clopidol and 3-nitro (Group 4).

Group	Days Withdrawn from Medicated Feed	Muscle Clopidol Concentration (ppm*)	Liver Clopidol Concentration (ppm)	Kidney Clopidol Concentration (ppm)
1	0	0	0	0
2	0	0	0	0
3	0	1.92 ± 0.65	8.67 ± 2.41	5.18 ± 0.51
4	0	1.32 ± 0.26	6.80 ± 1.78	4.15 ± 0.85

*ppm, parts *per* million

The effects of lincomycin on the assay of clopidol were assessed by assaying solutions containing clopidol with or without lincomycin. The assay response from the solution containing clopidol and lincomycin was the same as the assay response from the solution containing only clopidol.

2. Target Tissue and Marker Residue Assignment

A target tissue is not assigned for clopidol. NADA 034-393 contains summaries of studies supporting the approval of clopidol in broiler chickens (as published in the FEDERAL REGISTER (33 FR 17627) on November 26, 1968). These studies established clopidol as the marker residue (21 CFR 556.160).

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 lincomycin is not required in edible chicken tissues (as published in the FEDERAL REGISTER (55 FR 3208) on January 31, 1990; 21 CFR 556.360).

NADA 034-393 contains summaries of studies supporting the approval of clopidol in broiler chickens (as published in the FEDERAL REGISTER (33 FR 17627) on November 26, 1968). These studies established tolerances of 15 parts *per* million (ppm) in liver and kidney tissues and 5 ppm in muscle tissue for residues of clopidol (3,5-dichloro-2,6-dimethly-4-pyridinol; 21 CFR 556.160).

4. Withdrawal Period

A 0-day withdrawal period is assigned for the combined use of COYDEN® and LINCOMIX® (clopidol Type A medicated article and lincomycin Type A medicated article) when fed to broiler chickens as a Type C medicated feed containing 113.5 g/ton clopidol and 2 g/ton lincomycin.

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 period 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 clopidol and lincomycin on antimicrobial resistance among bacteria of public health concern in or on treated broiler chickens was not assessed.

D. Analytical Method for Residues

1. Determinative Method

   An FOI Summary was not prepared for the original approval of clopidol. The FR notice for the original approval of clopidol (as published in the FEDERAL REGISTER (33 FR 17627) on November 26, 1968) does not include a description of the analytical method for measuring clopidol residues in edible chicken tissues. The analytical method for clopidol is described in NADA 034-393.

   Because a tolerance for residues of lincomycin is not required for edible chicken tissues, an analytical method is not required.

2. Availability of Method

   The validated analytical method for the analysis of clopidol residues 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

IV. USER SAFETY

CVM did not require user safety studies for this approval.

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.

V. 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 COYDEN® and LINCOMIX® demonstrate that, when they are used according to the label, they are safe and effective as an aid in the prevention of cecal and intestinal coccidiosis caused by *E. 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 administered COYDEN® and LINCOMIX® 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 combination are not refillable.

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: 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 slow or prevent any potential for the 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 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.