Date of Approval: August 10, 2018

# FREEDOM OF INFORMATION SUMMARY

## ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-488

Avatec® and LINCOMIX®

(lasalocid 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 (ADAA) of 1996 feed combination for the indications listed in Section I.L.

Sponsored by:

Zoetis Inc.

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# I. GENERAL INFORMATION

## A. File Number

NADA 141-488

## B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

## C. Proprietary Names

Avatec® and LINCOMIX®

## D. Product Established Names

Lasalocid Type A medicated article and lincomycin Type A medicated article

## E. Pharmacological Categories

Avatec®: 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]

Avatec®: 90.7 g/lb of lasalocid (as lasalocid sodium)
LINCOMIX®: 20 or 50 g/lb of lincomycin (as lincomycin hydrochloride agricultural grade)

## H. How Supplied

Avatec® (lasalocid Type A medicated article): 50 lb bag
LINCOMIX® (lincomycin 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)**

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

    a. 68 to 113 g/ton of Avatec® for the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*.

    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.

## 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 Act also 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 safety of the combination of the lasalocid Type A medicated article and the lincomycin Type A medicated article on the effectiveness and target animal safety of the previously separately approved Avatec® and LINCOMIX® for use in broiler chickens, 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 provide 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.

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

| Proprietary Name | Sponsor | Indications | NADA (Original or supplemental approval date) | CFR Citation |
|---|---|---|---|---|
| Avatec® | Zoetis Inc. | for the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima* | 096-298 (October 8, 1976) | 21 CFR 558.113 |
| LINCOMIX® | Zoetis Inc. | for the control of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to lincomycin | 097-050 (July 13, 1977) | 21 CFR 558.325 |

## III. HUMAN FOOD 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 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 the lasalocid Type A medicated article and the lincomycin Type A medicated article on the human food safety of the previously separately approved Avatec® and LINCOMIX® for use in broiler chickens, 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 2):

**Table 2.** Establishment of the human food safety of individual drugs in this combination product.

| Active Pharmaceutical Ingredient | NADA | FOI Summary/FR Notice |
|---|---|---|
| lasalocid | 096-298 | FOI Summary dated August 6, 1982<br><br>41 FR 44381 dated October 8, 1976 |
| lincomycin | 111-636 | 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 097-505 contains summaries of studies supporting the approval of lincomycin in broiler chickens (35 FR 7300 dated May 9, 1970). NADA 096-298 contains summaries of studies supporting the approval of lasalocid in broiler chickens (41 FR 44381 dated October 8, 1976).

   b. Comparative Metabolism Studies

      CVM did not require comparative metabolism studies for this approval. NADA 097-505 contains summaries of studies supporting the approval of lincomycin in broiler chickens (35 FR 7300 dated May 9, 1970). NADA 096-298 contains summaries of studies supporting the approval of lasalocid in broiler chickens (41 FR 44381 dated October 8, 1976).

   c. Tissue Residue Depletion Studies

      For ADAA combination approvals, the Federal Food, Drug and Cosmetic Act (Section 512(d)(4)(A)) 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 lasalocid on the depletion or assay of lincomycin residues in edible chicken tissues in support of this approval. The agency did evaluate two studies that assessed the effect of lincomycin on the depletion and assay of lasalocid residues in edible tissues of chickens.

Study Title: Elimination of Lasalocid from the Tissues of Chickens Fed Lasalocid in Combination with Roxarsone and Lincomycin

Study Location: Nutley, NJ, USA

The objective of this study was to determine the concentration of lasalocid in edible tissues of chickens fed lasalocid, roxarsone[2] and lincomycin as a Type C medicated feed.

Three groups of chickens were used in this study (Table 3). Group 1 chickens (n = 112) were fed unmedicated feed for 56 days. Group 2 chickens (n = 40) were fed a Type C medicated feed containing 68 g lasalocid/ton and 45 g roxarsone/ton for 56 days. Group 3 chickens (n = 80) were fed a Type C medicated feed containing 68 g lasalocid/ton, 45 g roxarsone/ton, and 1.8 g lincomycin/ton for 56 days.

**Table 3.** Treatment groups and inclusion rates for lasalocid, roxarsone and lincomycin.

| Group | Lasalocid feed concentration | Roxarsone feed concentration | Lincomycin feed concentration |
|---|---|---|---|
| 1 | 0 g/ton | 0 g/ton | 0 g/ton |
| 2 | 68 g/ton | 45 g/ton | 0 g/ton |
| 3 | 68 g/ton | 45 g/ton | 1.8 g/ton |

Chickens from Groups 2 and 3 were slaughtered at 0, 1, 2 and 3 days withdrawn from medicated feed. Muscle, skin with fat, liver and kidney tissues were collected from four chickens from Group 2 and Group 3. The tissue samples were analyzed for lasalocid concentration by a thin-layer chromatography bioautographic method (Table 4).

**Table 4.** Mean (± standard deviation) lasalocid concentrations in edible tissues from broiler chickens consuming feed containing lasalocid and roxarsone (Group 2) or lasalocid, roxarsone and lincomycin (Group 3).

| Group | Days Withdrawn from Medicated Feed | Muscle Lasalocid Concentration (ppm) | Skin with Fat Lasalocid Concentration (ppm) | Liver Lasalocid Concentration (ppm) | Kidney Lasalocid Concentration (ppm) |
|---|---|---|---|---|---|
| 2 | 0 | <LOQ* | 0.37 ± 0.04 | <LOQ | <LOQ |
| 3 | 0 | <LOQ | 0.36 ± 0.03 | <LOQ | <LOQ |

[2] Approval of the roxarsone Type A medicated article, 3-NITRO, has been withdrawn (FR Vol. 78 No. 226 pg. 70062, dated 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 (lasalocid at 68 g/ton, 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 (lasalocid at 68 to 113 g/ton and lincomycin at 2 g/ton).

| Group | Days Withdrawn from Medicated Feed | Muscle Lasalocid Concentration (ppm) | Skin with Fat Lasalocid Concentration (ppm) | Liver Lasalocid Concentration (ppm) | Kidney Lasalocid Concentration (ppm) |
|---|---|---|---|---|---|
| 2 | 1 | <LOQ | 0.05 ± 0.00 | <LOQ | <LOQ |
| 3 | 1 | <LOQ | <LOQ | <LOQ | <LOQ |
| 2 | 2 | <LOQ | <LOQ | <LOQ | <LOQ |
| 3 | 2 | <LOQ | <LOQ | <LOQ | <LOQ |
| 2 | 3 | <LOQ | <LOQ | <LOQ | <LOQ |
| 3 | 3 | <LOQ | <LOQ | <LOQ | <LOQ |

*<LOQ, Less than the limit of quantification (*i.e.*, 0.05 ppm)

The effects of lincomycin on the assay of lasalocid were assessed in edible chicken tissues. Recovery of lasalocid from edible chicken tissues was similar between tissues fortified with lasalocid (0.1 ppm) and tissues fortified with lasalocid (0.1 ppm) and lincomycin (0.5 ppm).

Study Title: AVATEC + Roxarsone + Lincomycin Combination Clearance

The objective of this study was to determine the concentration of lasalocid in skin with fat tissue from chickens fed lasalocid, lincomycin and roxarsone as a Type C medicated feed.

Fifty-six chickens were fed a Type C medicated feed containing 113 g lasalocid/ton, 2 g lincomycin/ton, and 45.4 g roxarsone/ton for 56 days. At withdrawal days 0, 1, 2, 3 and 4, eight chickens were slaughtered. Skin with fat tissue samples were collected and analyzed for lasalocid concentration by a thin-layer chromatography bioautographic method (Table 5).

**Table 5.** Mean (± standard deviation) lasalocid concentrations in skin with fat from broiler chickens consuming feed containing lasalocid, lincomycin and roxarsone.

| Days Withdrawn from Medicated Feed | Skin with Fat Lasalocid Concentration (ppm) |
|---|---|
| 0 | 0.27 ± 0.11 |
| 1 | 0.07 ± 0.02 |
| 2 | <LOQ[†] |
| 3 | <LOQ |
| 4 | <LOQ |

[†]<LOQ, Less than the limit of quantification (*i.e.*, 0.05 ppm)

2. Target Tissue and Marker Residue Assignment

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

   NADA 096-298 contains summaries of studies supporting the approval of lasalocid in broiler chickens (41 FR 44381 dated October 8, 1976). These studies established skin with adhering fat as the target tissue and lasalocid as the marker residue (21 CFR 556.347).

3. Tolerance Assignments

   A tolerance for residues of lincomycin is not required in edible chicken tissues (55 FR 3208 dated January 31, 1990; 21 CFR 556.360).

   NADA 096-298 contains summaries of studies supporting the approval of lasalocid in broiler chickens. These studies established tolerances for lasalocid of 1.2 ppm in skin with adhering fat and 0.4 ppm in liver (FOI Summary dated February 20, 2001; 21 CFR 556.347).

4. Withdrawal Period

   A 0-day withdrawal period is assigned for the combined use of Avatec® (lasalocid) and LINCOMIX® (lincomycin) when fed to broiler chickens as a Type C medicated feed containing 68 to 113 g lasalocid/ton and 2 g lincomycin/ton.

## 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 lasalocid Type A medicated article and lincomycin Type A medicated article 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 lasalocid Type A medicated article and lincomycin Type A medicated article on the human intestinal flora was not assessed.

### D. Analytical Method for Residues

1. Determinative Method

   An analytical method for lasalocid is described in NADA 096-298 for lasalocid (FOI Summary dated February 20, 2001).

   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 lasalocid 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

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 Avatec® and LINCOMIX® demonstrate that, when they are used according to the label, they are safe and effective for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. brunetti, E. mivati,* and *E. maxima,* 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 Avatec® 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 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 diagnosis and

subsequently use this drug product, and 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.