Date of Approval: December 16, 2016

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-473

Stenorol® and LINCOMIX®

halofuginone hydrobromide and lincomycin

Type A Medicated Articles to be Used in the Manufacture of Type C Medicated Feeds

Broiler Chickens

For the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. brunetti*, *E. mivati/E. mitis*, 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

Sponsored by:

Huvepharma EOOD

TABLE OF CONTENTS

I. GENERAL INFORMATION

A. File Number

NADA 141-473

B. Sponsor

Huvepharma EOOD
5th Floor
3A Nikolay Haytov Str.
1113 Sofia, Bulgaria

Drug Labeler Code: 016592

US Agent:
Kelly W. Beers, Ph.D.
Director of Regulatory
525 Westpark Drive, Suite 230
Peachtree City, GA 30269

C. Proprietary Name

Stenorol® and LINCOMIX®

D. Product Established Name

Halofuginone hydrobromide and lincomycin

E. Pharmacological Category

Halofuginone hydrobromide: anticoccidial
Lincomycin: 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]

Halofuginone hydrobromide: 2.72 g/lb. (6 g/kg) halofuginone hydrobromide
Lincomycin: 20 or 50 g/lb. lincomycin

[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 is the subject of this approval.

H. How Supplied

Halofuginone hydrobromide: 50 lb. bag
Lincomycin: 50 lb. bag

I. Dispensing Status

VFD

J. Dosage Regimen

2.72 grams (3 ppm) halofuginone hydrobromide and 2 grams lincomycin per ton of Type C medicated feed

Feed continuously as the sole ration.

K. Route of Administration

Oral

L. Species/Class

Chickens, broilers

M. Indication

For the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. brunetti*, *E. mivati/E. mitis*, 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.

II. EFFECTIVENESS

In accordance with the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Animal Drug Availability Act (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.

Halofuginone hydrobromide, 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. brunetti*, *E. mivati/E. mitis*, and *E. maxima* (21 CFR 558.265(d)(1)(i)). Lincomycin, 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 in broiler chickens (21 CFR 558.325(e)(1)(i)). Effectiveness of each drug, halofuginone hydrobromide and lincomycin, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Huvepharma EOOD's approved NADA 130-951 for halofuginone hydrobromide and Zoetis Inc.'s approved NADA 097-505 for lincomycin to which Huvepharma EOOD has right of reference, respectively.

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

Halofuginone hydrobromide, 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. brunetti*, *E. mivati/E. mitis*, and *E. maxima* (21 CFR 558.265(d)(1)(i)). Lincomycin, 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 in broiler chickens (21 CFR 558.325(e)(1)(i)).

Under the provisions of ADAA, this original approval allows for the combination of halofuginone hydrobromide (as provided by Huvepharma EOOD) and lincomycin (as provided by Zoetis Inc.). Target animal safety for each drug, halofuginone

hydrobromide and lincomycin when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Huvepharma EOOD's approved NADA 130-951 for halofuginone hydrobromide and Zoetis Inc.'s approved NADA 097-505 for lincomycin to which Huvepharma EOOD has right of reference, respectively. The Agency has found no substantiated scientific issue relating to the target animal safety of halofuginone hydrobromide and lincomycin 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 130-951 for halofuginone hydrobromide (50 FR 33718, dated August 21, 1985), 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 097-505 for lincomycin contains summaries of studies supporting the approval of lincomycin in broiler chickens. The FOI Summary for the supplemental approval of halofuginone hydrobromide, NADA 130-951 dated March 8, 1991, contains a summary of residue chemistry studies in broiler chickens.

   b. Comparative Metabolism Study

      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. The FOI Summary for the supplemental

approval of halofuginone hydrobromide, NADA 130-951 dated March 8, 1991, contains a summary of residue chemistry studies in broiler chickens.

c. Tissue Residue Depletion Study

Title: "Broiler Tissue Residue Analysis for Accumulation of Lincomycin/ Halofuginone/ Roxarsone[2] Administered Through Feed." (Project No. 2370)

Study Dates: July 1986, to November 1986

In-Life Study Location: Fort Collins, Colorado

Analytical Laboratory Study Locations: Kalamazoo, Michigan and Vienna, Virginia

Objective: This study was conducted in accordance with the Good Laboratory Practices Regulations (GLPs; 21 CFR 58). The objective of the study was to quantitatively determine residue concentrations of halofuginone in liver tissue from broiler chickens fed lincomycin/halofuginone/roxarsone.

Experimental Design: 160 one-day old broiler cross chickens (80 males and 80 females) were randomly assigned to one of four pens. Animals were fed a complete feed ration containing 4 g/ton lincomycin, 3 ppm halofuginone and 45 g/ton roxarsone *via* hanging tube feeders. Feed was offered *ad libitum* for 45 days prior to placing birds on a control nonmedicated ration for the duration of the withdrawal period. Sixteen animals were fed a control nonmedicated diet for the entirety of the study. Animals were slaughtered at 0, 1, 2, 3, 4 and 5 days after withdrawal of medicated feed.

Measurements and Observations: Liver, muscle, and skin/fat samples were collected and analyzed for halofuginone hydrobromide and lincomycin. Halofuginone hydrobromide analysis was performed using a high-performance liquid chromatography (HPLC) method. Lincomycin analysis was conducted by a microbiological method.

Results: Lincomycin residues were below 0.1 ppm (sensitivity of the method) at days 0 and 1. Halofuginone hydrobromide residues were below the 0.16 ppm tolerance at withdrawal day 2 (Table 1).

[2] Approval of the roxarsone Type A medicated article, 3-NITRO, has been previously withdrawn (78 FR 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 (lincomycin at 4 g/ton, halofuginone at 3 ppm, and roxarsone at 45 g/ton) could be used to support assay noninterference and a 4-day withdrawal assignment for the two-way combination (lincomycin at 4 g/ton and halofuginone at 3 ppm).

Table 1. Mean (± std. deviation) halofuginone hydrobromide residues in liver from broiler chickens fed feed containing 4 g/ton lincomycin, 3 ppm halofuginone and 45 g/ton roxarsone.

Withdrawal Period (Days)	Halofuginone Concentration (ppm)
1	0.26 ± 0.15
2	0.06 ± 0.02
3	0.04 ± 0.01
4	0.02 ± 0.01
5	0.01 ± 0.01

Conclusion: A 4-day withdrawal period was calculated based on the halofuginone hydrobromide residues, the 0.16 ppm tolerance, and a statistical analysis with 95% confidence limits and 99% tolerance. The results demonstrate noninterference and confirm a 4-day withdrawal period.

2. Target Tissue and Marker Residue Assignment

   The target tissue for halofuginone hydrobromide is liver and the marker residue is parent drug (NADA 130-951 FOI Summary dated March 8, 1991). A target tissue and marker residue has not been established for lincomycin.

3. Tolerance Assignments

   The tolerance for parent halofuginone hydrobromide in chicken liver is 0.16 ppm (NADA 130-951 FOI Summary dated March 8, 1991; 21 CFR 556.308). A tolerance for residues of lincomycin is not required (21 CFR 556.360).

4. Withdrawal Time

   The residue depletion study summarized above confirms a 4-day withdrawal period for the combination use of halofuginone hydrobromide and lincomycin in broiler chickens.

C. Microbial Food Safety

Antimicrobial Resistance/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 Federal Food, Drug, and Cosmetic Act). Therefore, we did not 1) assess the impact of this combination of halofuginone hydrobromide and lincomycin on antimicrobial resistance among bacteria of public health concern in or on treated broiler chickens, or 2) assess the impact of residues of halofuginone hydrobromide and

lincomycin in edible food products from treated broiler chickens on human intestinal flora, or need to establish a microbiological acceptable daily intake.

D. Analytical Method for Residues

The tissue assay method for halofuginone hydrobromide is an HPLC method titled, "Analysis of an Anti-Coccidial Drug, Halofuginone, in Poultry Tissue". The tissue assay method for lincomycin is a microbiological method titled, "Standard Operating Procedure for a Tissue Residue Study in Broiler Chickens treated with Lincomycin, U-10, 149A". The methods are available from CVM, FDA, 7500 Standish Place, Rockville, MD 20855.

V. USER SAFETY

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

Halofuginone hydrobromide is an eye and skin irritant. Avoid contact with skin, eyes, and clothing.

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 and 21 CFR part 514. The data contained in the previously approved NADAs for Stenorol® and LINCOMIX® demonstrate that, when they 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/E. mitis*, 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 treated with Stenorol® 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 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 Federal Food, Drug, and Cosmetic 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.