Date of Approval: January 13, 2017

# FREEDOM OF INFORMATION SUMMARY

## ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-469

Stafac® and AMPROL®

virginiamycin and amprolium

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

Broiler Chickens

For prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin; and for the prevention of coccidiosis caused by *E. tenella* in broiler chickens.

For prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin; and for the prevention of coccidiosis where immunity to coccidiosis is not desired in broiler chickens.

Sponsored by:

Phibro Animal Health Corp.

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# I. GENERAL INFORMATION

## A. File Number

NADA 141-469

## B. Sponsor

Phibro Animal Health Corp.
GlenPointe Centre East, 3d floor
300 Frank W. Burr Blvd., suite 21
Teaneck, NJ 07666

Drug Labeler Code: 066104

## C. Proprietary Names

Stafac® and AMPROL®

## D. Established Name

virginiamycin and amprolium

## E. Pharmacological Category

Virginiamycin: antimicrobial
Amprolium: 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]

Virginiamycin: 20, 50, or 227 g/lb virginiamycin
Amprolium: 25% amprolium

## H. How Supplied

Virginiamycin (Stafac® 20 and Stafac® 50): 50 lb bag
Virginiamycin (Stafac® 500): 55 lb (25 kg), 1322 lb (600 kg), or 1764 lb (800 kg) bag
Amprolium: 50 lb bag

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[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.

**I. Dispensing Status**

VFD

**J. Dosage Regimen**

1. Feed continuously 20 g virginiamycin and 72.6 to 113.5 g (0.008-0.0125%) amprolium per ton of Type C medicated feed as the sole ration.

2. Feed 20 g virginiamycin and 113.5 to 227 g (0.0125-0.025%) amprolium per ton of Type C medicated feed.

**K. Route of Administration**

Oral

**L. Species/Class**

Broiler chickens

**M. Indications**

1. For prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin; and for the prevention of coccidiosis caused by *E. tenella* in broiler chickens.

2. For prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin; and for the prevention of coccidiosis where immunity to coccidiosis is not desired 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.

Virginiamycin, as provided by Phibro Animal Health Corp., has previously been separately approved for use in feed for broiler chickens for prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin (21 CFR §558.635(e)(1)(xiii)). Amprolium, as provided by Huvepharma EOOD, has previously been separately approved for use in feed for broiler chickens for the prevention of coccidiosis caused by *E. tenella* (21 CFR §558.55(d)(2)(iii)). Amprolium, as provided by Huvepharma EOOD, has previously been separately approved for use in feed for broiler chickens the prevention of coccidiosis where immunity to coccidiosis is not desired (21 CFR §558.55(d)(2)(vi)). Effectiveness of each drug, virginiamycin and amprolium, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Phibro Animal Health Corp.'s approved NADA 091-467 for virginiamycin and in Huvepharma EOOD's approved NADA 012-350 for amprolium to which Phibro Animal Health Corp. has right of reference.

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

Virginiamycin, as provided by Phibro Animal Health Corp., has previously been separately approved for use in feed for broiler chickens for prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin (21 CFR §558.635(e)(1)(xiii)). Amprolium, as provided by Huvepharma EOOD, has previously been separately approved for use in feed for broiler chickens for the prevention of coccidiosis caused by *E. tenella* (21 CFR §558.55(d)(2)(iii)). Amprolium, as provided by Huvepharma EOOD, has previously been separately

approved for use in feed for broiler chickens the prevention of coccidiosis where immunity to coccidiosis is not desired (21 CFR §558.55(d)(2)(vi)).

Under the provisions of ADAA, this original approval allows for the combination of virginiamycin (as provided by Phibro Animal Health Corp.) and amprolium (as provided by Huvepharma EOOD). Target animal safety for each drug, virginiamycin and amprolium, when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Phibro Animal Health Corp.'s approved NADA 091-467 for virginiamycin and in Huvepharma EOOD's approved NADA 012-350 for amprolium to which Phibro Animal Health Corp. has right of reference. The Agency has found no substantiated scientific issue relating to the target animal safety of virginiamycin and amprolium 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 have been established by data in NADA 091-467 for virginiamycin (46 FR 18966, dated March 27, 1981) and NADA 013-461 for amprolium (26 FR 4286, dated May 17, 1961).

### 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 091-467 contains summaries of studies supporting the approval of virginiamycin in broiler chickens (46 FR 18966, dated March 27, 1981). NADA 012-350 contains summaries of studies supporting the approval of amprolium in broiler chickens (26 FR 4286, dated May 17, 1961).

b. Comparative Metabolism Study

CVM did not require comparative metabolism studies for this approval. NADA 091-467 contains summaries of studies supporting the approval of virginiamycin in broiler chickens (46 FR 18966, dated March 27, 1981). NADA 012-350 contains summaries of studies supporting the approval of amprolium in broiler chickens (26 FR 4286, dated May 17, 1961).

c. Tissue Residue Depletion Study

For ADAA combination approvals, the FD&C 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 virginiamycin is not required in edible chicken tissues (21 CFR §556.750), there is no requirement to assess the effect of amprolium on the depletion or assay of virginiamycin residues in edible chicken tissues in support of this approval.

The Agency did evaluate a study that assessed the effect of virginiamycin on the depletion and assay of amprolium residues in edible tissues of chickens.

<u>Determination of Ethopabate and Amprolium content in tissues of broiler chickens medicated with elevated levels of AMPROL HI-E with and without virginiamycin and subjected to a zero withdrawal period</u>

Study No. V-M-4013-81

In-life Animal Phase Study Location: West Chester, PA, USA

Analytical Phase Study Location: Madison, WI, USA

Study Dates: January 14, 1981, to October 26, 1981

The objective of this study was to determine the concentration of amprolium and ethopabate in edible tissues of chickens fed 40 g virginiamycin/ton, 227 g amprolium/ton, and 72.6 g ethopabate/ton as Type C medicated feed.

Three groups of 22 chickens each (11 males, 11 females) were used in this study (Table 1). Group 1 chickens were fed unmedicated feed for 56 days. Group 2 chickens were fed virginiamycin, amprolium and ethopabate for 56 days. Group 3 chickens were fed amprolium and ethopabate for 56 days (Table 1).

Table 1. Treatment groups and inclusion rates for virginiamycin, amprolium and ethopabate.

| Group | Virginiamycin feed concentration | Amprolium feed concentration | Ethopabate feed concentration |
|---|---|---|---|
| 1 | 0 g/ton | 0 g/ton | 0 g/ton |
| 2 | 40 g/ton | 227 g/ton | 72.6 g/ton |
| 3 | 0 g/ton | 227 g/ton | 72.6 g/ton |

At the end of the 56-day medication period, the chickens were withdrawn from all feed for six hours and then slaughtered. Muscle, liver and kidney tissue samples were collected.

Tissues were assayed for amprolium according to the following method: "Determination of amprolium in eggs, meat, and meat products of chickens," Food Additives Analytical Manual, December 1, 1973.

Tissues were assayed for ethopabate according the following method: "GLC determination of ethopabate in chicken tissues by derivative formation," JAOAC, Volume 53, No. 3, pp. 461-464.

Mean tissue residue concentrations of amprolium are presented in Table 2. Although residues of ethopabate were assayed, ethopabate residues are not relevant to the approval of the current ADAA combination.

Table 2. Mean (± standard deviation) amprolium concentrations in tissues from broiler chickens fed unmedicated feed (Group 1); feed containing virginiamycin, amprolium, and ethopabate (Group 2); or feed containing amprolium and ethopabate (Group 3).

| Group | Liver Amprolium Concentration (mean ± standard deviation; ppm) | Kidney Amprolium Concentration (mean ± standard deviation; ppm) | Muscle Amprolium Concentration (mean ± standard deviation; ppm) |
|---|---|---|---|
| 1 | 0.08 ± 0.01 | 0.04 ± 0.00 | 0.09 ± 0.02 |
| 2 | 0.38 ± 0.15 | 0.27 ± 0.12 | 0.17 ± 0.03 |
| 3 | 0.32 ± 0.14 | 0.26 ± 0.07 | 0.23 ± 0.02 |

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 marker residue is codified for virginiamycin. Neither a target tissue nor marker residue is codified for amprolium.

3. Tolerance Assignments

   A tolerance is not required in chicken tissues for virginiamycin (21 CFR §556.750).

The tolerances for residues of amprolium in chicken tissues are 1 ppm in liver and kidney tissues and 0.5 ppm in muscle tissue (21 CFR §556.50).

4. Withdrawal Period

   A 0-day withdrawal period is assigned for broiler chickens continuously fed a Type C medicated feed containing 20 g virginiamycin/ton plus up to 227 g amprolium/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 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, we did not assess the impact of this combination of amprolium and virginiamycin on antimicrobial resistance development among bacteria of public health concern in or on treated broiler chickens.

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 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, we did not assess the impact of this combination of amprolium and virginiamycin on the residues of amprolium and virginiamycin in edible food products from broiler chickens on human intestinal flora and the need to establish a microbiological acceptable daily intake.

## D. Analytical Method for Residues

Because a tolerance for virginiamycin residues is not required in chicken tissues (21 CFR §556.750) and there is no official method for virginiamycin residues, it was not necessary to demonstrate that amprolium does not interfere with the assay of virginiamycin residues in chicken tissues.

The assay of tissues from parallel groups of chickens treated with amprolium and ethopabate or with virginiamycin, amprolium and ethopabate served to demonstrate that virginiamycin does not interfere with the assay of amprolium in chicken tissues. The official method for detection of amprolium residues is a

fluorimetric test. A description of the official method is filed in the Food Additives Analytical Manual that is on file at the Center for Veterinary Medicine, FDA, 7500 Standish Place, Rockville, MD 20855.

## V. USER SAFETY

The product labeling does not contain any information regarding safety to humans handling, administering, or exposed to the Type C medicated feed.

## 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 Stafac® and AMPROL® demonstrate that, when used according to the label, they are safe and effective
1) for prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin; and for the prevention of coccidiosis caused by *E. tenella* in broiler chickens, and 2) for prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin; and for the prevention of coccidiosis where immunity to coccidiosis is not desired in broiler chickens. Additionally, data demonstrate that residues in food products derived from broiler chickens treated with Stafac® and AMPROL® 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 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.