FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-470
Stafac® and Avatec®

virginiamycin and lasalocid sodium
Type A Medicated Articles to be Used in the Manufacture of Type C Medicated Feeds

Broiler and fryer chickens

For the prevention of necrotic enteritis caused by Clostridium perfringens susceptible to virginiamycin and for the prevention of coccidiosis caused by Eimeria tenella, E. necatrix, E. acervulina, E. brunetti, E. mivati and E. maxima.

Sponsored by:
Phibro Animal Health Corp.
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I. GENERAL INFORMATION

A. File Number

NADA 140-470

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 Name

Stafac® and Avatec®

D. Established Name

Virginiamicin and lasalocid sodium

E. Pharmacological Category

Virginiamicin: antimicrobial
Lasalocid sodium: anticoccidial

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 Products

Virginiamicin: 20, 50, or 227 g/lb virginiamicin
Lasalocid sodium: 90.7 g/lb lasalocid sodium

H. How Supplied

Virginiamicin (Stafac® 20 and Stafac® 50): 50 lb bag
Virginiamicin (Stafac® 500): 55 lb (25 kg), 1322 lb (600 kg), or 1764 lb (800 kg) bag
Lasalocid sodium: 50 lb. bag

I. Dispensing Status

VFD

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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 are the subject of this approval.
J. Dosage Regimen

Feed continuously 20 g virginiamycin and 68 to 113 g lasalocid sodium per ton of Type C medicated feed as the sole ration.

K. Route of Administration

Oral

L. Species/Class

Broiler and fryer chickens

M. Indication

For the prevention of necrotic enteritis caused by *Clostridium perfringens* susceptible to virginiamycin and for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. brunetti, E. mivati* and *E. maxima*.

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 (558.635(e)(1)(xiii)). Lasalocid sodium, as provided by Zoetis Inc., has previously been separately approved for use in feed for broiler and fryer chickens as an aid in the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. brunetti, E. mivati* and *E. maxima* (558.311(e)(1)(i)). Effectiveness of each drug, virginiamycin and lasalocid sodium 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 Zoetis Inc.’s approved NADAs 096-298 for lasalocid sodium to which Phibro Animal Health Corp. has right of reference.
Because virginiamycin and lasalocid sodium each has at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that virginiamycin plus lasalocid sodium provide appropriate concurrent use for the intended target population. The use of virginiamycin plus lasalocid sodium 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 and fryer 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 (558.635(e)(1)(xiii)). Lasalocid sodium, as provided by Zoetis Inc., has previously been separately approved for use in feed for broiler and fryer chickens as an aid in the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. brunetti*, *E. mivati* and *E. maxima* (558.311(e)(1)(i)).

Under the provisions of ADAA, this original approval allows for the combination of virginiamycin (as provided by Phibro Animal Health Corp.) and lasalocid sodium (as provided by Zoetis Inc.). Target animal safety for each drug, virginiamycin and lasalocid sodium, 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 Zoetis Inc.’s approved NADA 096-298 for lasalocid sodium, 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 lasalocid sodium 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 096-298 for lasalocid sodium (41 FR 44381, dated October 8, 1976), and NADA 091-467 for virginiamycin (46 FR 18966, dated March 27, 1981).

B. Residue Chemistry

1. Summary of Residue Chemistry Studies
   a. Total Residue and Metabolism Study

   CVM did not require total residue and metabolism studies for this approval. NADA 096-298 contains summaries of studies supporting the approval of lasalocid sodium in broiler and fryer chickens (41 FR 44381, dated October 8, 1976), and NADA 091-467 contains summaries of studies supporting the approval of virginiamycin in broiler chickens (46 FR 18966, dated March 27, 1981).

   b. Comparative Metabolism Study

   CVM did not require comparative metabolism studies for this approval. NADA 096-298 contains summaries of studies supporting the approval of lasalocid sodium in broiler and fryer chickens (41 FR 44381, dated October 8, 1976), and NADA 091-467 contains summaries of studies supporting the approval of virginiamycin in broiler chickens (46 FR 18966, dated March 27, 1981).

   c. Total Residue and Depletion Study

   (1) Residue Interference Study in Tissues from Broiler Chickens Medicated with Virginiamycin and Roxarsone\(^2\) in Combination with Monensin, Lasalocid sodium or Amprolium (Study III)

\(^2\) 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 (virginiamycin at 20 g/ton, roxarsone at 45.4 g/ton, and lasalocid sodium at 113.5 g/ton) could be used to support assay noninterference and a zero-day withdrawal.
The study was divided into two locations to accommodate the administration of radiolabel drug to one group of the test birds.

i. Study No. V-4003-78

Study Location: West Chester, Pennsylvania

ii. Study No. V-4002-76

Study Location: Chestertown, Maryland

A total number of 162 one-day old chicks (81 males and 81 females) were used. Administration of medicated feed began at 2 days of age.

Table 1. Composition and schedule of medicated feeds provided to chickens.

<table>
<thead>
<tr>
<th>Study No. / Type of Ration</th>
<th>Composition of Ration</th>
<th>Duration of Feeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>V-4003-78 / Starter Ration</td>
<td>45.4 g/ton roxarsone 113.5 g/ton lasalocid sodium</td>
<td>Days 2-37</td>
</tr>
<tr>
<td>V-4003-78 / Finisher Ration</td>
<td>20 g/ton $^{14}$C-virginiamycin 45.4 g/ton roxarsone 113 g/ton lasalocid sodium</td>
<td>Days 38-57</td>
</tr>
<tr>
<td>V-4002-76 / Starter Ration</td>
<td>23 g/ton virginiamycin 45.4 g/ton roxarsone 80 g/ton salinomycin</td>
<td>Days 2-30</td>
</tr>
<tr>
<td>V-4002-76 / Finisher Ration</td>
<td>23 g/ton virginiamycin 45.4 g/ton roxarsone 80 g/ton salinomycin</td>
<td>Days 31-54</td>
</tr>
<tr>
<td>V-4002-76 / Withdrawal Ration</td>
<td>Non-medicated</td>
<td>1 to 6 days</td>
</tr>
</tbody>
</table>

The chickens in Study No. V-4003-78 were slaughtered at 0 days (4 hours after cessation of medicated feed). Muscle, liver, kidneys, and skin/fat samples were collected and analyzed for $^{14}$C -virginiamycin equivalents using combustion/scintillation counting. The chickens in Study V-4002-76 were slaughtered at 0, 1, 5, and 6 days after withdrawal of medicated feed. Abdominal skin/fat was collected and analyzed for lasalocid sodium. Lasalocid sodium analysis was performed using a bioautographic method (LOQ = 0.01 ppm). Lasalocid sodium residues at zero withdrawal were below the codified tolerance of 1.2 ppm. $^{14}$C -virginiamycin residues at zero withdrawal were below the safe concentrations of 30 ppm in muscle, 90 ppm in liver, and 60 ppm in skin/fat (described in FOI Summary for NADA 091-467). The results demonstrate assay non-interference and confirm a 0-day tissue withdrawal period.

assignment for the two-way combination (virginiamycin at 20 g/ton and lasalocid sodium at 113.5 g/ton).
Table 2. Mean $^{14}$C-virginiamycin equivalents in muscle, liver, and skin/fat at zero day withdrawal from broiler chickens fed feed containing 23 g/ton virginiamycin, 45.4 g/ton roxarsone, and 113.5 g/ton lasalocid sodium (Study No. V-4003-78).

<table>
<thead>
<tr>
<th>Tissue</th>
<th>$^{14}$C-equivalents (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>0.01</td>
</tr>
<tr>
<td>Liver</td>
<td>0.19</td>
</tr>
<tr>
<td>Skin/Fat</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Table 3. Mean lasalocid sodium residues in skin/fat at zero withdrawal from broiler chickens fed feed containing 23 g/ton virginiamycin, 45.4 g/ton roxarsone, and 113.5 g/ton lasalocid sodium (Study No. V-4002-76).

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Lasalocid sodium Concentration (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin/Fat</td>
<td>0.03</td>
</tr>
</tbody>
</table>

2. Target Tissue and Marker Residue Assignment

No reassessments of target tissue and marker residue were needed for this approval. The target tissue for lasalocid sodium in chickens is skin/fat and the marker residue is parent lasalocid sodium. Neither a target tissue nor a marker residue is codified for virginiamycin in chickens.

3. Tolerance Assignments

A tolerance for parent lasalocid sodium in chicken skin/fat is 1.2 ppm (21 CFR §556.347). A tolerance for residues of virginiamycin in broiler chickens is not required (21 CFR §556.750).

4. Withdrawal Time

The residue depletion data summarized above confirms a 0-day withdrawal period for the combination use of lasalocid sodium and virginiamycin in broiler chickens.

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 Federal Food, Drug, and Cosmetic Act). Therefore, we did not assess the impact of this combination of lasalocid and
virginiamycin on antimicrobial resistance development among bacteria of public health concern in or on treated broiler and fryer chickens.

2. Impact 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 assess the impact of this combination of lasalocid and virginiamycin on the residues of lasalocid sodium and virginiamycin in edible food products from broiler and fryer chickens on human intestinal flora and the need to establish a microbiological acceptable daily intake.

D. Analytical Method for Residues

An analytical method is not needed for virginiamycin because total residues of virginiamycin in broiler chicken tissues at zero day withdrawal do not exceed the safe concentrations for virginiamycin.

Refer to NADA 096-298 for lasalocid sodium for the approved regulatory analytical method. The method is available from the Center for Veterinary Medicine, FDA, 7500 Standish Place, Rockville, Maryland, 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 Avatec® demonstrate that, when they used according to the label, they are safe and effective for the prevention of necrotic enteritis caused by Clostridium perfringens susceptible to virginiamycin and for the prevention of coccidiosis caused by Eimeria tenella, E. necatrix, E. acervulina, E. brunetti, E. mivati and E. maxima in broiler and fryer chickens. Additionally, data demonstrate that residues in food products derived from broiler and fryer chickens treated with Stafac® and Avatec® 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.